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Urethral Instability: Current Pathophysiological Concept

Key Words

Urethral instability · Urodynamics · Filling cystometry · Urethral pressure variations

Abstract

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, its value for the 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.

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Introduction

The role of urodynamics in diagnosis as well as evaluation of treatment of 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 a rise in detrusor pressure during filling cystometry (i.e. detrusor overactivity). Filling cystometry is performed to register the impact of natural bladder filling on the 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 (relieving 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 a setting which is as physiological as possible. 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 subcommittee 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 to do so in the past [4]. Urethral pressure measurement is still first and foremost a research tool [5].

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In this paper we 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 dealt with routinely in clinical practice, the observation of urethral pressure variations during filling cystometry is studied intensively by several authors. In 1981, the ICS committee on standardization 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 to redefine URI and stated that further investigations would be necessary to formulate a proper definition [7]. In 2002, a revision of the terminology of lower urinary tract function was published by the standardization subcommittee of the ICS [4]. Again, the subcommittee 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. The 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 [8] reported on 11 patients with incontinence and large postvoid residual volumes. 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 [9] noticed voiding without any detectable rise in detrusor pressure in a few females, apparently by reflex relaxation of their urethral sphincter mechanisms. Conceptually, a disturbance of this reflex may result in inappropriate relaxation and URI may be an occasional cause of incontinence in females.

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 a 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 [20] used a lower cutoff value and defined pressure variations of >10 cm water as URI. Wise et al. [21] 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-min period.

Pathological urethral pressure variations should be distinguished from physiological urethral pressure variations according to Vereecken [22]. The focus should be 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 s), 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 indicate pathological urethral pressure variations.

McLennan et al. [23] defined URI by recording resting urethral pressure for 2 min after 50 ml bladder filling and, later on, during filling cystometry. Urethral pressure variations were calculated as the ratio of Δ 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-min resting period. Using this definition, URI occurred in 12.6%, whereas if in the same group the definition of pressure changes of >15 cm water was used, the prevalence increased to 31%. Four patterns of urethral pressure variations during a 2-min resting cystometry (with 50 ml bladder filling) as well as during filling cystometry were observed by McLennan et al. They observed (1) resting pressure variations without detrusor activity, (2) resting

URI as well as DO during filling, (3) no resting URI but detrusor contraction preceded by a fall in urethral pressure (so-called type II DO), and (4) resting URI and type II DO. Because it is well-known that with the exception of patients with detrusor-sphincter dyssynergia, the urethra always relaxes prior to a detrusor contraction, urethral abnormality (e.g. URI) may be the primary disorder in patients with complaints of an overactive bladder. 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 [13] showed URI in 14.4% of 173 patients with a history of incontinence. In 52% of these patients, no concomitant DO was present. Urethral pressure variations over 35 cm water provoked urgency. Weil et al. [14] found URI associated with DO in 27% of 427 patients. Most investigators suggest a link between URI and DO. A close association between URI and DO was also reported by Clarke [16]. 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. In contrast to the assumed association of URI and pathology, Kulseng-Hansen [19] found urethral pressure variations of more than 20 cm water in more than 50% of normal females. Hence, other than in previous definitions, he considered urethral pressure variations of more than 10, 15 or 20 cm water not as pathological anymore. The urethral pressure variation (Δ MUP) was calculated as the difference between the highest and the lowest MUP observed during 1 min 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 [10] studied 71 female patients with complaints of urge, stress or mixed incontinence. URI was seen in 66%. DO was reported to have occurred in 24% of all patients.

Symptoms Related to URI

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 there are only few studies, often there is a focus on the role of urethral pressure variations or URI in sensory storage symptoms [24]. It is getting increasingly clearer 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 such as dysuria, frequency or urgency). However, DO was more strongly associated with urge urinary incontinence, nocturia and urgency than URI [14]. According to Vereecken and Das [13] pressure variations, exceeding 35 cm water, may provoke urgency. In contrast, Wise et al. [21] 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. Venema and Kramer [10] already stated that URI is an expression of sensory urge. URI may also be an important element in dysfunctional voiding. It may cause the urge sensation during filling and the staccato voiding phase in patients with dysfunctional voiding [25].

An Attempt to Define URI Based on Our Experience

At the Urology Department of the Leiden University Medical Center, Leiden, The Netherlands, filling cystometry in females is performed with the MMS UD-2000 (Medical Measurement Systems, Enschede, The Netherlands) and a Gaeltec CTU/2E/L-4 12F (Gaeltec, Dunve-

Fig. 1. Urethral pressure changes are present in all three urethral pressure measurements. The finding is defined as major URI, exceeding an amplitude of more than 30 cm water.

gan, Isle of Skye, UK) catheter with 3 urethral sensors and 1 bladder sensor. The space between each urethral sensor is 7 mm; the distance between bladder pressure sensor and mid-urethral pressure sensor is 50 mm. The mid-urethral pressure sensor is positioned at the maximum urethral pressure. Urethral and detrusor function are monitored, both during filling and voiding. Three urethral sensors are necessary to rule out artefacts due to movements of the catheter in the urethra during filling. Pressure changes caused by movement of the catheter will give a shift in recorded pressures. Only pressure changes measured by all 3 urethral sensors are considered relevant, because they are caused by pressure changes in the major part of the urethra itself. We define URI when urethral pressure variations of more than 15 cm water are observed in all three urethral recordings. We have the impression that classification into 'minor' urethral pressure changes (16–30 cm water) and 'major' (>31 cm water) may be important for clinical practice. Slow periodical urethral pressure variations with durations of more than 10 s and with low amplitude are considered as normal. The impact of presence or absence of DO for defining URI remains controversial in the literature. We do

not consider the presence or absence of DO of importance to define URI. A review of the literature did not reveal clear understanding of whether sphincter EMG recording is necessary for diagnosing URI. Therefore, we do not take EMG recordings into consideration for the diagnosis of URI. Most studies on urethral pressure variations during filling cystometry use only one urethral sensor. We measure urethral pressure variations with 3 urethral pressure sensors to rule out artefacts. The use of only one urethral pressure sensor may give incorrect recordings and result in a false prevalence for the presence of 'truly' URI. In order to achieve optimal localization of the pressure sensors in the urethra, at least one sensor has to be positioned at the site of the maximum urethral pressure. In the minority of cases it is impossible, as a result of urethral anatomy, to obtain urethral registration with all 3 sensors.

Figure 1 shows the urodynamic recording of both urethral and detrusor behaviour during filling cystometry. Urethral pressure variations are clearly visible on all three urethral pressure recordings. Concomitant DO is not present in this female patient with symptoms of an OAB.

Fig. 2. Urethral pressure variations are only seen in 2 urethral recordings. This observation is not defined as URI.

Fig. 3. A pathologically low FSF is seen at the start of major urethral pressure changes. In this patient DO is also present throughout the filling phase.

Fig. 4. FSF and a drop in urethral pressure are observed at 15 ml of bladder filling, together with an involuntary rise in detrusor pressure, indicating DO. During the filling phase urethral pressure changes are seen without concomitant DO.

Only when urethral pressure variations are seen on all three urethral pressure recordings, we define the observation as URI. In this patient, therefore, with urethral pressure changes only in the proximal and mid-urethral sensor, the observation is not defined as URI. If only one urethral pressure sensor had been used in the same patient, the observation might well have been named URI (fig. 2).

A clear drop in urethral pressure together with a non-physiological early first sensation of filling (FSF) at 60 ml is demonstrated as shown in figure 3. With continuing filling, following FSF (a sensory parameter indicated by the patient), more pronounced URI is observed. In this patient, DO is also present. Figure 3 illustrates clearly that decreases in urethral pressure are synchronic with rises in detrusor pressure. In figure 4, the FSF and a drop in urethral pressure are observed, together with an involuntary rise in detrusor pressure, indicating DO. Later during the filling phase, urethral pressure variations are seen without concomitant DO.

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 micturition 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 the literature varies, due to the use of different definitions, together with inappropriate urethral pressure recordings. To rule out artefacts, such as movement or incorrect position of the urethral pressure sensor, the use of more than one urethral pressure sensor is advo-

cated. Only in this way are correct urethral pressure recordings achieved and can results 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 symptoms of patients 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 prevention of urinary tract infection and need to be considered as pathophysiological [27]. McLennan et al. [23] published on the significance of urethral pressure measurements during filling cystometry. When accepting certain urethral pressure variations as pathological (URI), differentiation into 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. To rule out artefacts, such as movement of the pressure sensor during urodynamic testing, the use of more than one urethral sensor is to be preferred. Only in this way are more accurate recordings achieved.

The prevalence of urethral pressure variations and the clinical significance are a matter for discussion. The review from the literature shows different prevalences in different studies with different definitions for URI. This makes you 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. [3] noticed that urethral pressure changes can be important for the sensation of urgency. The sensation of urgency was better synchronized with a 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.

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 the 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 significantly shorter functional urethral length could be found in women with unstable urethra behaviour [23]. Chaliha et al. [28] 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. They suggested that for a correct assessment of urethral function, DO has to be treated first. Earlier reports also found morphological changes of the urethra in patients with DO compared to those with normal urodynamic testing. A smaller total urethral diameter and circumference as a result of the loss of smooth muscle thickness was found. This could result in a decrease in urethral resistance, enabling urine to enter the bladder neck and so to initiate detrusor contraction. It remains, however, unclear whether differences in urethral function are the result of DO rather than its cause [29]. By studying 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 the urethral function leads the bladder function more than the other way around is supported by the concept of the guarding reflex [1].

In therapy evaluation such as in sacral neuromodulation (SNM), it was evident that the delay in FSF was correlated with the success of the treatment [30]. In our data on SNM therapy, a disappearance 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

puddendal blockage with lignocaine whereas these observations were absent before the pudendal blockage [32]. This observation draws attention to 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 an early pathological 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 the literature.

The origin of URI is still not fully understood. Kenton et al. [33] observed no increase in urethral pressure 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. 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 parasympathetic nerves.

We experienced that SNM therapy is capable of abolishing URI [31]. By stimulation of sacral nerves at the level of the sacral foramen, both afferents and efferents are activated. Only A- α fibres are stimulated; the threshold for stimulation of C fibres and A- δ fibres is too high. It is generally accepted that the modulating effect of SNM is generated by stimulation of the afferent nerves. Somatic and sensory fibres 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 fibres from bladder, urethra and the anorectal region [35]. These afferent pudendal and pelvic fibres 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 successfully treated SNM patients.

Conclusions

The presence of urethral pressure variations during filling cystometry has been well documented by various investigators. Unfortunately, so far this has not led to a better understanding of the phenomenon. Different definitions for different types of patterns of pressure variations 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 such as the guarding reflex illustrate the 'leading' role of urethral function. Morphological changes within the urethra together with sympathetic activity might explain urethral pressure fluctuations.

Too often investigations have 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 related studies on bladder function only, we recommend the 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 standardized method.

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