Urethral function in overactive bladder syndrome

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CHAPTER 3

CONTINUOUS URETHRAL PRESSURE MEASUREMENTS: A SYSTEMATIC LITERATURE ANALYSIS

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INTRODUCTION

Normal adult lower urinary tract (LUT) storage function requires a detrusor muscle that is relaxing and adapting to volume -increment with low pressure. On the other side, the outlet should remain closed, to prevent incontinence. Passive as well as muscle outlet factors play a role and, crudely; 'outlet muscles' should remain contracted, to a certain degree during urine storage phase, to ensure continence(1, 2). Urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as the overactive bladder syndrome (OAB), urge syndrome or urgency-frequency syndrome(3)

OAB is urodynamically associated with both presence and absence of detrusor overactivity (DO). Urethral pressure variations (UPV) are observable with continuous intra urethral pressure measurement and have been observed during urodynamic investigation as well in association with DO in patients with lower urinary tract symptoms (LUTS) (4, 5) as in individuals without LUTS(6, 7) The clinical relevance of UPV, also referred to as urethral instability, in the pathophysiology of OAB has remained controversial since the initial reports,(8-10) Furthermore it is unknown whether patients with UPV have specific symptoms, hidden in-, or separate from OAB, and as a consequence specific management for patients with 'significant' UPV is not yet available.

In the period 1978-1996 various studies have described UPV and discussed whether this is an isolated entity apart from DO or not, without an unambiguous conclusion.(5, 8-12). The international continence society (ICS) defined unstable urethra in 1981 as the condition where urinary loss is solely caused by a fall in urethral pressure(13). The condition defined by this definition is however rare and as a consequence various propositions for definition have been made. The ICS did reach a new compromise for the definition and for a relatively long time, no studies have been performed on this subject. Recently, the International Consultation on Incontinence Research Society (ICI-RS) recommended new clinical research to be performed on this topic.(14)

We have performed a systematic review of the available evidence with regard to UPV with the aim to provide an overview of the measurement methods and the (proposed) definitions as well as the reported prevalence. The scientific quality of the studies was systematically evaluated.

On the basis of this systematic review we suggest for urodynamic practice and future research and hope that this may contribute to targeted management and therefore may optimize the treatment of patient suffering from OAB or LUTS.

METHODS

In September 2014, the electronic databases Pubmed, Embase, Web of Science, Cochrane, Central, Cinahl, Academic Science Premier, Science Direct and WileyOnline were searched using the search strategies as shown in Fig. 1. The articles were screened by title, abstract or by full article, when necessary, to select the studies that met the predefined selection criteria. Initial selection criteria were; Urethral pressure variations / urethral instability as the predominant outcome, performed with adult female patients, without relevant neurological conditions in a cohort study or randomized controlled trial and reported full text available in English, German, French or Dutch. We excluded case studies or cohorts less than ten patients and expert reviews were also not included. Reference screening and citation tracking were performed on the identified articles.

All authors have independently reviewed and scored all full text papers that met the inclusion criteria, according to the STARD-checklist(15). Consensus about methodological quality was obtained in an open discussion meeting according to Oxford Level of Evidence (LoE, version March 2009).

The items reviewed were selection bias, description and specifications of urodynamic evaluation (type and position of catheter used, position of patients, filling speed, EMG), informed consent, approval by medical ethics committee, definition of urethral pressure variation and reported prevalence.

RESULTS

487 articles were identified and no paper was excluded because of the language. Among the list of excluded papers were papers in Japanese, Chinese, Spanish and Italian, but the main topic of these papers was not about urethral pressure variations or had a too small sample size. Five papers were excluded because they reported on non-adult patients

also.(16-19). Six papers were excluded because of mixed gender studies. (9, 20-23). Six expert opinion reviews were excluded(24-28) (29). When multiple papers were published on the basis of a single patient cohort, only one paper of those, with the largest cohort, was included, others were considered duplicate and excluded.(7, 29-31) Twenty-five papers met all predefined selection criteria and were included. Only two of the studies(32, 33) were performed after approval of local ethics committee and with informed patient consent.

The reported incidence of UPV has varied between 2 and 95%.(34, 35) Definition of UPV, as well as measurement methods and techniques, patient position, cystometry and catheter type and position show a large variety and are shown in tables 1 and 2. The papers report studies of weak methodological quality with Oxford LoE scores of 3B or 4, an overview is shown in table 3(4-6, 8, 12, 16, 18, 32-50). Striking is that all studies have reported and or concluded an association of DO/OAB with UPV although patients selection at entry or at evaluation may have played a role in this.

Table 3.1 Reported (urodynamic) technique (N studies =25)

Catheter used	N	Position sensor	N
Dual microtip sensor, (1 urethra)	18	Ventral	2
2 separate catheters	2	Lateral	6
3 sensors urethra	2	Not specified	17
5 sensors urethra	1		
Open water filling	1		
Microtip, not specified	1		

Table 3.2 Overview study types and variables of urodynamic investigation

Study	Study type	Filling rate	Postion of patients	EMG
Bergman et al (36)	Prospective Cohort	60 ml/min	NA	N
Demoulin et al (37)	Limited cohort	50 ml/min	NA	Y (some)
Farrell and Tynski(38)	Retrospective case series	80 ml/min	Sitting + standing	Y
Groenendijk et al. (34)	Prospective case series	NA	NA	Y
Hilton (33)	Retrospective case series	Fixed vol. 250ml	Supine	N
Kulseng-Hanssen (18)	Retrospective case series	Fixed 100+50ml/min	Semirecumbent	NA
Kulseng-Hanssen and Kristoffersen (6)	Selected cases	Fixed 100+30ml/min	Semirecumbent	NA
Low et al. (39)	Selected cases	20 ml/min	Supine	N
McLennan et al. (4)	Prospective case series	80 ml/min	Sitting	N
Penttinen (43)	Retrospective case series	50 ml/min till 300ml	Supine	N
Plevnik and Janez (44)	Retrospective case series	NA	Supine	N
Sorensen (45)	Retrospective case series	NA	NA	Y (nothing reported)
Sorensen et al. (46)	Retrospective case series	Diuresis	NA	Needle
Sand et al. (35)	Prospective case series	"medium filling"	Supine + sitting	Y
Schaer et al. (47)	Case series	60 ml/min	Supine	N
Sorensen et al. (40)	Prospective case series	Fixed vol. 250 ml	Supine + sitting	Y
Tapp et al. (32)	Prospective case series	Fixed vol. 250 ml	Supine	N
Ulmsten et al. (41)	Prospective case series	50 ml/min	Sitting + standing	N
Venema and Kramer (48)	Retrospective selected cases	50 ml/min	Sitting + standing	Y
Vereecken (5)	Retrospective case series	NA	NA	Y
Vereecken et al. (49)	Case series	28 ml/min	Supine + sitting	Y
Vereecken and Das (8)	retrospective selected casses	28 ml/min	Sitting	Y
Versi and Cardozo (50)	Prospective case series	Fixed vol. 250 ml	NA	N
Weil et al. (12)	Prospective case series	50 ml/min	Supine	N

Table 3.3 Overview Oxford Level of Evidence, definitions and reported prevalence

Study	Oxford LoE	Inclusion def.	Exclusion def.	Definition UPV	Prevalence
Bergman et al (36)	3B	poor	poor	probably one type	39% ?
Demoulin et al (37)	4	poor	selected series	types / patterns	?
Farrell and Tynski(38)	4	selected	selected	patterns	73% UDI
Groenendijk et al. (34)	3B	yes	no	16-30 or >30cm-H2O	95%
Hilton (33)	4	poor	no	continuous	not dichotomous
Kulseng-Hanssen (18)	4	no	no	>20cmH2O	20%
Kulseng-Hanssen and Kristoffersen (6)	4	no	no	continuous	?
Low et al. (39)	4	selected	selected	>20cmH2O drop	selected
McLennan et al. (4)	3B	consecutive	consecutive	ratio, 4 patterns	13%
Penttinen (43)	4	consecutive?	No	posthoc 3 patterns	63%
Plevnik and Janez (44)	4	no	no	posthoc 10-40cm-H2O	67%
Sorensen (45)	3B	poor	poor	all variation	?
Sorensen et al. (46)	4	poor	healthy	all variation	?
Sand et al. (35)	4	selected	selected	all variation	2%
Schaer et al. (47)	3B	selected	no	15-30 and 30-130cmH2O	17%
Sorensen et al. (40)	4	selected	healthy	posthoc 3 types	?
Tapp et al. (32)	4	yes	yes	variable	not dichotomous
Ulmsten et al. (41)	4	consecutive	consecutive	posthoc 3 types	12%
Venema and Kramer (48)	4	yes	poor	>15cmH2O	?
Vereecken (5)	4	no	posthoc	posthoc typing	8%
Vereecken et al. (49)	4	no	selected	>15cmH2O	18%
Vereecken and Das (8)	4	no	selected	>15cmH2O	14%
Versi and Cardozo (50)	3B	yes	poor	posthoc	14%
Weil et al. (12)	3B	poor	poor	posthoc	16%
Wise et al. (16)	4	poor	poor	ratio	42%

DISCUSSION

The generalizability of the performed studies is limited because all studies have been performed with very heterogeneous and poorly defined –retrospective single centre- patient populations with poorly defined in- and exclusion criteria. The results of the studies are difficult to combine since a wide variety of measurement methods and patient populations is reported. Clinical relevance of UPV and consequences for management of patients with LUTS are yet to be established and we suggest that this is of relevance since epidemiological studies in the US and in Europe show prevalence figures for OAB of 16% to more than 50% of the population(51-53). Estimated is that 29.8 million adults aged ≥40 years in the United States have bothersome OAB symptoms(54) but not all affected people seek medical attention.(55) In the year 2007, estimated total national cost in US of OAB with urinary incontinence was $65.9 billion, with projected costs of $76.2 billion in 2015 and $82.6 billion(56). OAB syndrome has a negative impact on health-related quality of life (QoL)(57, 58) and the worse the symptoms, the larger the negative effect(59).

Considering fundamental and clinical research, there exists a phenomenon of UPV, apart from detrusor overactivity, which may be a distinguishable pathophysiological entity, probably within the cohort of persons with OAB. That the normal outlet remains closed during urine storage is not only dependent on outlet anatomy and passive mechanics but also on muscular contraction activity. Especially when related to physical stress with intra- abdominal pressure rises, the passive properties play a role. With regard to the muscle activity component of urinary continence, both voluntary striated pelvic muscle as well as autonomic internal sphincter / bladder -neck smooth muscle activity is relevant. Voluntary pelvic -striated- muscle relaxation –physiologically- allows (or initiates) smooth muscle internal sphincter relaxation and detrusor dome muscle contraction that, in turn, opens the urethra and prompts passage of urine. The internal sphincter and detrusor dome act as autonomic antagonists under the 'guidance of' somatosensory innervated pelvic muscles'.(2) Failure of the detrusor to relax during the entire storage phase is a deviation from normal physiology referred to as detrusor over activity (DO), observable as pressure increment(s) during cystometry. Failure of the bladder outlet to remain closed (maybe observable as UPV) in the storage phase will result in symptoms of LUT dysfunction and or urinary incontinence.

Although the clinical relevance may be obvious continuous intra urethral pressure during storage is technically not easy to measure. An element of continuous urethral closure is intra urethral pressure and continuous intra urethral pressure measurement could give information about urethral muscular closure function alike continuous detrusor pressure measurement gives information about detrusor relaxation and volume adaptation. However, because the closed urethra during LUT storage phase has no lumen, pressure cannot be measured in the physical sense. Intra-urethral pressure recording, with contemporary available techniques can, at best only, provide surrogate observations and provide circumstantial evidence, for the urethral closure function. The techniques that are applied for intravesical (or rectal –abdominal) pressure measurement are fundamentally imperfect to measure the physics of urethral closure. As a consequence, those results are prone to intrinsic artefacts, or just 'only artefacts' in the eyes of its opponents. The catheter by itself, the measuring fluid and orientation of catheter measuring opening, or the sensor-stiffness or orientation, are causing artefacts simply by their position and the space that is occupied inside the urethral lumen. Moreover also a slightly moving or displacing sensor may mimic UPV because the 'pressure' inside the urethra is unequally distributed, even when the total muscle activity around the outlet is not changing during the time of that movement. In the studies performed with multiple urethral pressure sensors, all sensors register urethral pressure variations simultaneously, they have however been best recognized at the point of maximal urethral pressure.

Small amplitude pressure variations have arbitrarily always been considered normal. Abrupt pressure variations have been interpreted as movement artefacts. Bearing this in mind evaluation of research articles reporting UPV should include much caution. We have nevertheless evaluated the existing evidence for UPV, for measuring techniques and methods to evaluate outlet function during storage and UPV.

In the included studies three different patterns are consistently reported: Slow wave pattern UPV's, with relatively small amplitude; UPV's of varying amplitude, prior to DO and third: Fast and brief UPV's with relatively large ($>$ 40cmH_2O) amplitude, observed during the entire filling cystometry.

The discussion whether or not UPV are a realistic phenomenon is probably not the question to debate. Just like the observation of DO during filling cystometry in normal persons that not bother or perceive symptoms, UPV's can be observed in healthy individuals without obvious LUTS. The fact that the detrusor muscle can fail to (adapt and) relax during bladder

filling makes it plausible that its antagonist, the smooth urinary sphincter and or the striated urethral sphincter may fail to maintain contracted, and clinical studies that falsify this are never published. The focus of attention should be to distinguish between the phenomenon within normal limits and phenomenon leading to signs and symptoms and or pathophysiology. The current scientific evidence is too weak to answer this question in a way that allows generalizable conclusions.

For the future research for UPV we suggest that clinical urodynamic testing is standardised. Patients should be investigated in sitting position during continuous, medium (30-50mL/min) filling rate cystometry. Continuous urethral pressure should be registered, ventrally oriented in the urethra (12 o'clock position) minimally at the point of maximal urethral pressure, however we acknowledge that it is difficult to maintain urethral pressure measurement at a fixed point in the urethra with the commonly available techniques. Certainly improved techniques to monitor (active and or passive maintenance of) urethral closure function during cystometry are much needed in this regard. Future research may validate if single urethral sensor is as representative as multisensory urethral catheters in diagnosing urethral pressure variations.

CONCLUSION

Systematic analysis or the literature regarding UPV shows large variation in technique and low Oxford level of evidence research. Different patterns and definitions of urethral pressure variations / urethral instability have been reported. Despite the poor methodological quality of the performed studies and the inherent measurement problems, UPV may be regarded a –potentially pathophysiological- entity of its own within cohorts of patients with OAB. We suggest that future prospective research needs to be performed with better-standardized urodynamic technique and focuses on the fast and brief pattern of UPV. Obviously, a well-defined patient population and urodynamic measurement methods according to ICS standard of good urodynamic practises are of utmost relevance. Studies should be performed in both symptomatic and asymptomatic patients. Urodynamic observations should be combined with validated clinical questionnaires. Further research should aim to better instigate personalised management for patient suffering OAB and more systematic evaluation of UPV may help in this regard.

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