W7: Detrusor underactivity: detection and diagnosis

Workshop Chair: Gommert van Koeveringe, Netherlands

20 October 2014 09:00 - 12:00

Start	End	Topic	Speakers
09:00	09:20	Detrusor underactivity, a new condition for known symptomatology?	• Christopher Chapple
09:20	09:40	Detrusor underactivity and aging	• Gommert van Koeveringe
09:40	10:00	Male patients with detrusor underactivity	• Matthias Oelke
10:00	10:20	Female patients with detrusor underactivity	• Gommert van Koeveringe
10:20	10:30	Questions	All
10:30	11:00	Break	None
11:00	11:20	How can we find selective parameter combinations?	• Kevin Rademakers
11:20	11:40	Which approach is necessary to detect patients at risk?	• Matthias Oelke
11:40	12:00	What are future steps necessary to confirm the condition, develop therapy, and follow up after treatment?	• Christopher Chapple • Matthias Oelke • Kevin Rademakers • Gommert van Koeveringe

Aims of course/workshop

Detrusor underactivity has gained increasing scientific and clinical interest since it became obvious that a substantial number of female or male patients suffer from this bladder condition. The key speakers of this workshop are intensively involved in new research initiatives within this unexplored field. They will present and discuss the known facts concerning the diagnosis of detrusor underactivity. Which invasive or non-invasive tools to assess contractility are currently available? How can we differentiate detrusor underactivity from bladder outlet obstruction? How do we define the patients with detrusor underactivity and what are differences in assessment of male and female patients?

Handout

W7 Detrusor underactivity: detection and diagnosis

Monday 20th October 2014
09:00-12:00
Chair:

- Gommert van Koeveringe, Netherlands

Speakers:

- Christopher Chapple, United Kingdom
- Matthias Oelke, Germany
- Kevin Rademakers, Netherlands

Aims & Objectives:
Detrusor underactivity has gained increasing scientific and clinical interest since it became obvious that a substantial number of female or male patients suffer from this bladder condition. The key speakers of this workshop are intensively involved in new research initiatives within this unexplored field. They will present and discuss the known facts concerning the diagnosis of detrusor underactivity. Which invasive or non-invasive tools to assess contractility are currently available? How can we differentiate detrusor underactivity from bladder outlet obstruction? How do we define the patients with detrusor underactivity and what are differences in assessment of male and female patients?

Detrusor underactivity, a new condition for known symptomatology?	Voiding dysfunction or LUTS can be due to either obstruction or detrusor underactivity or a combination of these conditions. Until recently only little attention was given to the condition detrusor underactivity. This changed a few years ago due to possible new treatment options. Professor Chapple will introduce this other view on voiding dysfunction and explain how symptomatology and conditions might be related. For further reading on this subject, we recommend: *Osman NI, Chapple CR, Abrams P, et al. Detrusor underactivity and the underactive bladder: A new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. Eur Urol 2014;65:389–98.* and *van Koeveringe GA, Vahabi B, Andersson KE, et al. Detrusor underactivity: Aplea for new approaches to a common bladder dysfunction. Neurourol Urodyn 2011;30:723–8. PubMed PMID: 21661020. Epub 2011/06/11. eng.* Both published articles are added tot this handout in the appendix.
Detrusor underactivity and aging	The ethiology of detrusor underactivity is often not know. With increasing age, it has been seen that the incidence of detrusor underactivity increased. However whether Detrusor underactivity is a normal effect of ageing or whether other pathology is necessary in combination with ageing to cause the condition, is still uncertain. Dr van Koeveringe will address this subject in more detail and recommends further reading using the following articles: *van Koeveringe GA, Rademakers KL, Birder LA, Korstanje C, Daneshgari F, Ruggieri MR, Igawa Y, Fry C, Wagg A. Detrusor underactivity: Pathophysiological considerations, models and proposals for future research. ICI-RS 2013. Neurourol Urodyn. 2014 May 16. doi: 10.1002/nau.22590. [Epub ahead of print]PMID:24839258*

	And the publication of *Osman et al* mentioned earlier.
Male patients with detrusor underactivity	Prof. Oelke will explain the factors playing a role in the ethiology, detection, diagnosis and possible treatment of detrusor underactivity in males. Further reading is recommended of the articles mentioned above and added in the appendix.
Female patients with detrusor underactivity	Dr van Koeveringe will explain the factors playing a role in the ethiology, detection, diagnosis and possible treatment of detrusor underactivity in females. Further reading is recommended of the articles mentioned above and added in the appendix.
How can we find selective parameter combinations?	Drs Rademakers will discuss current literature on parameters that might be used for detection and diagnosis in combination with new data from ongoing research projects
Which approach is necessary to detect patients at risk?	As the use of pressure flow analyses is invasive and expensive, there is a need tob e able te detect patients at risk. Prof. Oelke will discuss which approach might be useful both for the clinician analysing voiding dysfunction in his or her patient and for future use in clinical trials.
What are future steps necessary to confirm the condition, develop therapy, and follow up after treatment?Appendix:	A panel of all speakers will discuss with the audience their view on what might be necessary to develop for the near future. In preparation fort his discussion we recommend to read the article of *van Koeveringe et al 2014* mentioned above and added in the appendix.

Appendix:

Neurourology and Urodynamics 30:723–728 (2011)

Detrusor Underactivity: A Plea for New Approaches to a Common Bladder Dysfunction

G.A. van Koeveringe, MD, PHD[1,*] B. Vahabi, PHD[2] K.E. Andersson, MD, PHD[3] R. Kirschner-Herrmans, MD, PHD[4] and M. Oelke, MD, PHD[5]

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Aims: Detrusor underactivity (DU) is defined by the International Continence Society as a contraction of reduced strength and/or duration resulting in prolonged or incomplete emptying of the bladder but has yet received only little attention. The purpose of this report is to summarize the ICI-RS meeting in Bristol in 2010 exploring current knowledge on DU and outline directions for future research. **Methods:** A think tank discussion was held and the summary of discussions was presented to all ICI-RS participants. This report is based on the final discussions. **Results:** The understanding of the pathophysiology, epidemiology, assessment, and treatment of DU remains rudimentary. DU is defined by pressure-flow analysis but no consensus exists regarding which of the available formulae should be used for quantification of detrusor work. DU is likely to be multifactorial. Aging causes a decay in detrusor activity but other concomitant causes, either myogenic or neurogenic, may aggravate the problem resulting in decrease of detrusor contractility. No effective pharmacotherapy for the condition exists. Only a few surgical therapeutic strategies have been explored, such as neuromodulation and skeletal muscle myoplasties. Consequently, the management of affected individuals remains unsatisfactory. **Conclusions:** Future directions recommended by the ICI-RS panel include assessment of pathogenesis by developing novel animal models in addition to new non-invasive tests allowing longitudinal trials. Furthermore, optimizing the existing evaluation algorithms to support standard testing for DU and further epidemiological studies to quantify the size of the problem are required for the development of future treatment modalities. *Neurourol. Urodynam. 30:723–728, 2011.* © 2011 Wiley-Liss, Inc.

Key words: bladder outlet obstruction; detrusor contractility; detrusor underactivity; non-obstructive voiding dysfunction; underactive bladder; urinary retention

INTRODUCTION

Detrusor underactivity (DU) has yet received only little scientific attention. This is illustrated by a Medline search for publications between 1980 and 2010 using the terms "detrusor underactivity" and "underactive bladder" that revealed 93 and 80 publications, respectively, resulting in a total of 165 different articles during the last 30 years. In contrast, "detrusor overactivity" and "overactive bladder/OAB" had as many as 1,223 and 2,688 hits, respectively.

The incidence and prevalence of a condition is highly dependent on both definition and available diagnostic tests. The availability of treatment modalities greatly determines the need for a thorough diagnostic work-up and vice-versa. Improved tests and treatment options will eventually lead to a higher degree of differentiation within the general condition. Until recently, the only available treatments for DU had been clean intermittent catheterization or drug therapy. Drugs, especially directly or indirectly acting parasympathomimetics, remain contentious due to low efficacy and high prevalence of side-effects.[1] During the past decade, new treatment modalities have become available, such as neuromodulation, neurostimulation, or latissimus dorsi muscle transposition. The focus on bladder reconstruction using tissue engineering warrants more research with regard to the mechanisms of detrusor control and contractility.

The purpose of this report, based on discussions during the 2nd ICI-RS meeting in Bristol in June 2010, is to critically summarize and structure the current knowledge of DU and outline suggestions for future research.

METHODS

Step 1

An outline for a think tank discussion was prepared by the two chairmen (G.vK. and M.O.) based on a literature review. The topic: "Detrusor underactivity" or "underactive bladder" was discussed by the participants of the think tank with regard to etiology, pathophysiology, epidemiology, assessment, and treatment.

Conflict of interest: none.
Christopher Chapple led the review process.
Abbreviations used: BOO, bladder outlet obstruction; DU, detrusor underactivity; ICI-RS, International Consultation on Incontinence—Research Society; ICS, International Continence Society; PG, prostaglandin; UAB, underactive bladder.
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Received 6 February 2011; Accepted 9 February 2011
Published online 15 June 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/nau.21097

Step 2

The think tank session was summarized and a hierarchy of importance for future research subjects was proposed and combined in a presentation for all ICI-RS participants.

Step 3

The summary presentation together with structured future research subjects was discussed by a large group of experts and audio-recorded. Additional suggestions were noted and integrated into the proceedings.

Step 4

The results of this process are summarized in this article and highlighted in boxes.

RESULTS

Definition

The ICS (2002) defines DU as “a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying, and/or failure to achieve complete bladder emptying within a normal time span.”[2] This definition has not been changed in the latest terminology report[3] and contains two different pathophysiological causes, namely (1) too weak detrusor contraction force and (2) too short detrusor contraction duration. It was lately suggested that impaired contraction velocity may also contribute to DU.[4] DU is a urodynamic diagnosis based on pressure-flow and characterized by low-pressure, poorly sustained detrusor contraction in combination with low urinary flow.[5] In contrast, the term underactive bladder (UAB) has not been defined by the ICS but is often used synonymously with DU.[6]

It is not likely that all causes of DU are based on the same pathophysiology; therefore, grouping all causes in one term (DU) appears unsatisfactory. A differentiation based on the existence of neurogenic causes, as in detrusor overactivity, might be useful, which will then result in terms like neurogenic detrusor underactivity (NDU) or idiopathic detrusor underactivity (IDU). If reduced contraction strength, contraction duration, and contraction velocity reflect different pathophysiologies it seems justified using different terms for better differentiation. However, investigations on different causes remain sparse, therefore, the current ICS definition should be used until proven wrong.

The ICS definition also implies that DU is associated with urinary signs, that is, prolonged bladder emptying time and/or post-void residual urine. It remains unknown how long normal voiding time is and what the associated voiding volumes are. Additionally, it remains to be defined whether DU is always associated with post-void residuals and how much post-void residual justifies the diagnosis. It is also debatable whether particular symptoms or quality-of-life aspects should be added to the definition.

> *Recommendation*: The ICI-RS panel proposes to adhere to the original ICS definition but to further specify DU by adding the condition in which it occurs (e.g., DU with bladder outlet obstruction or DU with neurogenic bladder dysfunction). The term UAB should not be used. Retrospective urodynamic database analyses in patients with voiding dysfunction could clarify the association between reduced contraction strength and duration and could also determine whether, and to what extent, DU is linked to incomplete bladder emptying (reduced voiding efficiency), reduced sensation, and lower urinary tract symptoms.

Epidemiology

Longitudinal studies on detrusor contractility are not available. Urodynamic data suggest that DU and post-void residuals are associated with aging.[7–9] Of men and women aged >60 years, 22.1% and 10.8%, respectively, report difficulties with bladder emptying.[10] DU was found in nearly two-thirds of incontinent institutionalized elderly[11] with impaired detrusor contractility considered the most common cause. However, age-related decrease of detrusor contractility as the primary contributor to impaired bladder emptying has not been conclusively demonstrated. A modest decline of detrusor contractility was found in older, healthy, otherwise urodynamically normal people. Menopause may also contribute to DU because ovariectomy results in axonal degeneration and loss of detrusor muscle cells.[12]

DU is common in patients with neurogenic bladder dysfunction, for example, multiple sclerosis,[13] Parkinson’s disease,[14] dementia, diabetes mellitus,[15] sacral neuropathy, or cerebral stroke.[16] DU can also be caused by iatrogenic nerve damage, for example, after laparoscopic prostatectomy, hysterectomy, or other surgical interventions in the small pelvis.[17] Women with hip fractures or large-joint orthopedic surgery are also at risk of acute urinary retention[18] indicating that anesthesia in combination with concomitant DU may decompensate bladder function post-operatively.

More than half of men aged >50 years have lower urinary tract symptoms[19] and bladder outlet obstruction (BOO) has been implicated as the main cause. Recent analyses indicates urinary retention may also occur in the absence of BOO and coexisting morbidity such as DU. Detrusor failure may follow prolonged untreated BOO but the hypothesis that DU worsens over time with untreated BOO has recently been questioned.[20] Thus, prostate surgery may be of little benefit in men with DU.[5]

Female BOO is rare in older women especially without the history of previous peri-urethral surgery, absence of high-grade urogenital prolapse, or major atrophic vaginitis. Thus, the presence of voiding dysfunction and urinary retention in women strongly suggests the presence of DU as the underlying cause.

Many risk factors (drugs, constipation, immobility) may contribute to DU. Several drugs, especially antimuscarinics, compete with acetylcholine at muscarinic receptors.[21] But also neuroleptics,[22] calcium channel antagonists,[23] and α-receptor agonists[24] increase retention, yet the relationship to DU is not always obvious. Anesthesia may also be a risk factor for DU. Constipation leads to anal distension and reduces detrusor contractility.[25] Immobile individuals are more likely to be in retention.[26] Another risk factor of DU is recurrent urinary tract infection; however, data originate from animal studies[27] and clinical data in humans are lacking.

> *Recommendation*: Considering the amount of patients presumably affected more research should be targeted towards epidemiology of DU. The ICI-RS panel proposes to conduct longitudinal trials to quantify the amount of affected, preferably with non-invasive tests.

Pathophysiology

The understanding of the pathogenesis of DU remains rudimentary; however, it is likely to be multifactorial. It is recognized that detrusor contractility diminishes with aging although not everyone develops clinically relevant DU. It is therefore conceivable that concomitant conditions may cause DU. Individuals in whom the main cause is thought to be an age-related decrease in detrusor contractility and are without detectable other causes may be labelled as "primary" or "idiopathic" DU. In other individuals, the presence of a detectable relevant condition (e.g., diabetes, BOO, ethanol abuse) may lead to "secondary" DU. Similar to DO, the pathogenesis of DU may be related to myogenic and/or neurogenic factors.

New insights into the intricate interplay of neural, myogenic, and other cell types of the bladder, of which the interstitial cells and the peripheral neurones are of particular interest,[28] have resulted in several new hypotheses about the pathogenesis of bladder dysfunction.

Myogenic mechanisms. Individuals with DU may experience a greater decline in detrusor contractility than people with normal aging. Studies in diabetic bladders have shown "disruptive cells" similar to those found in DU.[29] Additionally, a decrease in the muscle to collagen ratio,[30,31] widened spaces between muscle cells,[32] age-related increased levels of circulating norepinephrine,[33] and a decrease of M3-muscarinic receptor density[34] have been found. Changes in the properties and density of calcium and potassium channels and gap junctions may also be part of myogenic-mediated DU. All factors may contribute to altered excitation–contraction coupling mechanisms of muscle cells and result in reduced autonomous activity of the bladder. In normal bladders, autonomous detrusor activity has been detected during the filling phase of the micturition cycle and is associated with generation of bladder sensation.[35] Decreased bladder sensations have been associated with DU in the elderly and suggest a more complex etiology of DU.

Neurogenic mechanisms. Neurogenic mechanisms leading to DU may be separated into those resulting from direct changes in the efferent limb of the micturition reflex, those of the afferent signals initiating the reflex, and those associated with a defect integrative control.

The micturition reflex is controlled by spino-bulbo-spinal pathways which integrate the sacral parasympathetic nucleus, the pontine micturition center and higher cortex centers. Activation and maintenance of the micturition response are dependent upon normal relay of sensory information from the bladder to higher brain centers. Within the dynamic interplay of bladder control, it may be postulated that sensory dysfunction contributes to DU. It has been shown that increasing age leads to decreased responses within the brain regions involved in interpreting the afferent sensory input from the bladder.[36] In diabetic patients, DU is associated with impaired Aδ and C fiber bladder afferent pathways.[15] Changes in urothelial receptor function and neurotransmitter release as well as in the sensitivity and coupling of the suburothelial interstitial cell network, which are vital for the relay of sensory information from the bladder, may also lead to DU.

In addition to sensory dysfunction, specific efferent alterations may also promote DU. It has been postulated that inadequate or insufficiently sustained neurogenic stimulation of the detrusor may play a role.[36] However, decreased neurogenic stimulation[36] and reduced density of acetylcholinesterase-positive nerves[37] in aging and obstructed bladders were found. Reduced/absent efferent stimulation of the detrusor will result in DU or detrusor acontractility and subsequent detrusor muscle de-differentiation and impaired detrusor function.

Recommendation: The ICI-RS panel proposes to develop animal model(s) to investigate the pathophysiology of DU. Additionally, longitudinal trials are necessary to reveal the pathogenesis and, as urodynamic investigations seem to be unsuitable for this purpose, new non-invasive tests should be developed.

Assessment

The lack of a standard test to diagnose and quantify DU contributes to limited knowledge. Three algorithms, which are all based on computer-urodynamic investigation and quantification of detrusor pressure during voiding, have been suggested to quantify detrusor power:

1. *Griffiths' Watt factor*: quantification of detrusor power with a complicated formula consisting of detrusor pressure during voiding, contraction speed, and bladder volume at each point of micturition, expressed as W/m^2.[38] Detrusor power varies during voiding, single calculations are usually offered on urodynamic evaluation sheets, for example, maximum detrusor power (W_{max}) or detrusor power at maximum flow (W_{Qmax}). However, it remains controversial which of the calculations and what threshold value should be used. Expert opinion suggested using a W_{max} threshold value of $7.0\,W/m^2$.
2. *Schäfer's detrusor-adjusted mean PURR factor (DAMPF)*: detrusor power can grossly be quantified as very weak, weak, normal, or strong if linearized passive urethral resistance (linPURR) is drawn into the Schäfer nomogram.[39] The length of linPURR determines detrusor strength.
3. *Abrams' bladder contractility index (BCI)*: quantification of detrusor power/contractility can be derived from Schäfer's linPURR lines and calculated by the formula: $BCI = pdetQmax + 5Qmax$.[40] $BCI > 150$ describes strong contractility, 100–150 normal contractility, and <100 weak contractility.

All algorithms were developed for adult men but have not been validated in women. Furthermore, it is unknown if all three algorithms equally describe bladder power, what the particular threshold values are to define DU, and if results of the individual tests are interchangeable with each other. Another dimension of the assessment problem arises when taking into account that detrusor power decreases age-dependently[41]; this would imply different threshold values in different age groups. To our knowledge, no correlations with clinical parameters (e.g., post-void residual volume or symptoms) have been made in order to compare symptoms or signs of DU with computer-urodynamic detrusor contraction parameters. This correlation would be helpful in defining clinically meaningful threshold values.

The vast majority of computer-urodynamic investigations were performed as in-office procedures; however, there is ongoing debate about their universal validity because relevant urethral sphincter activity may interfere with voiding. A recently published study in patients with voiding disorders showed that 84% of patients with acontractile detrusors during office urodynamics had detrusor contractions during ambulatory urodynamics.[42] It therefore seems valuable to compare results of conventional in-office urodynamics with ambulatory urodynamics to exclude relevant iatrogenic changes.

All mentioned algorithms can only be applied if computer-urodynamic investigation has been performed. Therefore, quantification of detrusor work is limited to people who are willing to undergo urodynamics and would most probably exclude the majority of people in epidemiological studies. It would seem useful to establish alternative tests to diagnose DU. Detrusor biopsies have been proposed accordingly[32]; however, biopsies are invasive and appear unsuitable for the majority of patients. Furthermore, single bladder biopsies might not be representative for the entire detrusor wall and morphological changes might not be consistently associated with functional changes. Hence, there is a strong need to develop valid non-invasive tests to diagnose or even quantify detrusor power. These tests could be ultrasonic-derived measurements (e.g., measurement of detrusor wall thickness or ultrasonic-estimated bladder weight) and might prove that DU is associated with reduced bladder muscle mass. Ultrasound studies of the detrusor during storage or voiding may show contraction movement patterns[35] indicating DU as well. It might even be possible to establish a combination of non-invasive tests to be analyzed in a neural network. However, research has not yet focused on non-invasive tests.

Recommendation: The ICI-RS panel proposes as a priority to define the most suitable (urodynamic) algorithm for DU. This algorithm should be the basis for further investigations of detrusor power/contractility. Retrospective urodynamic database analyses could clarify the differences between published algorithms and could correlate urodynamic results with clinical data. Comparison of in-office and ambulatory urodynamics should clarify the value of psychological biases. Later, investigations should clarify whether non-invasive tests are suitable to replace conventional urodynamics.

TABLE I. Drugs Used for the Treatment of Overflow Incontinence/Detrusor Underactivity, Adapted From Ref. 46, With Authors' Permission

Drug class (bold) and drugs	Level of Evidence [1–5]	Grade of Recommendation [A–D]
α-Adrenoreceptor antagonists		
Alfuzosin	4	C
Doxazosin	4	C
Prazosin	4	C
Terazosin	4	C
Tamsulosin	4	C
Phenoxybenzamine	4	NR
Muscarinic receptor agonists		
Bethanechol	4	D
Carbachol	4	D
Acetylcholinesterase		
Distigmine	4	D
Other drugs		
Baclofen	4	C
Benzodiazepines	4	C
Dantrolene	4	C

Assessment of drugs according to the Oxford Center of Evidence-based Medicine.
Level of Evidence 4 = case-series or poor quality cohort and case–control studies; Grade of Recommendation C = level 4 studies or extrapolations from level 2 or 3 studies; Grade of Recommendations D = level 5 evidence or troublingly inconsistent or inconclusive studies of any level.
NR, not recommended.

Treatment

It is initially important to define what should be treated and therapy should target a clinical problem (e.g., post-void residuals, recurrent urinary tract infections). Treatment may focus on increasing bladder contractility, decreasing BOO, or both.

The lack of a standard test to diagnose and quantify DU contributes to limited knowledge of the underlying mechanisms and, therefore, treatment of the underlying pathophysiology is currently impossible. If pragmatic treatments are properly evaluated using adequate tools pre- and post-treatment more insight might be generated into the pathophysiological mechanisms of DU. Moreover, the response to treatment of patients with different pre-treatment characteristics might also provide insight into the causative factors of the problem.

Voiding is supposed to be initiated by an adequate relaxation of pelvic floor and urinary sphincter; a failure of those structures inhibits pelvic floor relaxation and causes voiding dysfunction as well as inhibition of detrusor contraction (guarding reflex).[43] Therefore, pelvic physiotherapy to adequately relax the pelvic muscles seems to be one of the first treatment choices. However, little research has been directed towards treating hypo- or acontractile bladders with pelvic floor physiotherapy. Several indications can be found in current, mainly pediatric literature.[42,44,45]

Based on new insights and identification of different signaling pathway systems within the bladder wall an increasing number of pharmacological compounds can be evaluated for enhancement of detrusor strength or stimulation of sensation. Theoretically, all drugs that improve decreased sensation (and increase afferent activity) or drugs that increase the detrusor contractile force could be useful. Additionally, agents that decrease outflow resistance restoring an appropriate balance between detrusor strength and urethral resistance could be used alternatively.

Current standard pharmacotherapy includes the use of muscarinic receptor agonists (e.g., bethechanol) or choline esterase inhibitors (e.g., distigmine). However, analyses demonstrate little beneficial effects of these drugs and an unfavorable effect/side-effect profile.[1,46] Efficacy of other drugs is also inadequate (Table I).

The effect of capsaicin and resiniferatoxin to stimulate bladder activity via activation of transient receptor potential (TRP) channel V1 should make small molecule TRPV1 agonists interesting drugs if they do not desensitize afferent bladder nerves. The effects of other TRP channel activators may also be worthwhile studying.[47,48] According to pre-clinical data such agents may stimulate activity in urothelial and myogenic afferent pathways and have direct effects on detrusor contractility.[47]

Prostaglandin (PG) E_2, acting through four types of EP receptors (EP1–EP4), can both increase detrusor contraction and relax the urethra.[49] PGE_2 does not only stimulate detrusor contraction directly but may also enhance the efficacy of contraction-mediating transmitters (acetylcholine and ATP). EP1 and EP3 receptors seem to mediate the excitatory bladder effects of PGE2, both on afferent activity and on smooth muscle, and EP2 receptors are known to mediate bladder and urethral relaxation. In addition, PGE_2 may increase afferent activity both by stimulating the urothelial and myogenic afferent pathways. Thus, this agent appears ideal for stimulating bladder contraction. Indeed, intravesical instillation of PGE_2 or other prostanoids were shown to be efficacious[50] but associated with side-effects (e.g., uterine contraction). It may be possible to eliminate adverse events without losing the efficacy of PGE_2. Drugs which stimulate both EP3 and EP2 receptors simultaneously would have an interesting pharmacokinetic profile for patients with DU under the supposition that they are selective for the bladder. There is an obvious risk of inducing DO/OAB and it is questionable if such drugs work if orally administered.

Both neurostimulation[51,52] and neuromodulation[53] have been used for the treatment of DU. Several mechanisms of neuromodulation have been proposed, such as correction of a disturbed reflex action[54] or using a rebound phenomenon[55] in the CNS by stimulation of the afferent pathways to the areas in the brain that control bladder and sphincter function. However, a direct efferent effect of the sacral nerve stimulation on the control mechanisms in the detrusor remains possible and is a challenging field to be studied in the near future.[56]

If an acontractile bladder is diagnosed and less invasive treatments have failed, more invasive surgical reconstructive procedures have been successfully applied to restore bladder function. Latissimus dorsi muscle transposition has been successfully used by Stenzl et al.[57] and results of a multicenter study have been described by Gakis et al.[58] Besides reconstructive procedures, tissue engineered constructs or injected stem cells[59] might be considered as an option for restoring the contractile function of the bladder.

The pragmatic treatment choice remains clean intermittent catheterization if patients reject evaluation and unfavorable therapies with side-effects or limited chances for cure.[60] Current innovations in the field of catheter coating, sterilization, and packaging, together with a low chance of trauma and side-effects, can make this treatment acceptable for life-time application.

Recommendation: The ICI-RS panel proposes that treatment options for DU should increase detrusor strength or bladder sensation or should decrease bladder outlet resistance. When adequate tests are available, pre- and post-treatment analysis could clarify whether treatment responses fit to a pathophysiological model. This may provide a deeper insight into the pathophysiology of DU.

SUGGESTIONS FOR RESEARCH

The most urgent problems associated with DU are:

1. Establishment of a generally accepted (urodynamic) test or algorithm for sensitive quantification of detrusor work and precise definition of DU.
2. Replacement of the urodynamic test by establishment of a valid, accurate, and sensitive non- or minimally invasive test for broader use.
3. Quantification of DU in the general (asymptomatic) population and (symptomatic) patients. Special attention should be directed towards concomitant conditions which mimic symptoms of or appear together with DU.
4. Development of adequate animal models to study the pathophysiology of DU.
5. Definition of new therapeutic targets and testing of novel pharmacological principles to improve bladder contractility and sensation.

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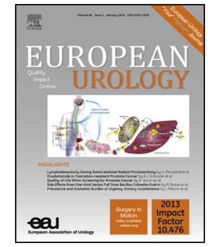

European Association of Urology

Platinum Priority – Review – Voiding Dysfunction

Editorial by Karl-Erik Andersson on pp. 399–401 of this issue

Detrusor Underactivity and the Underactive Bladder: A New Clinical Entity? A Review of Current Terminology, Definitions, Epidemiology, Aetiology, and Diagnosis

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Article info

Article history:
Accepted October 12, 2013
Published online ahead of print on October 26, 2013

Keywords:
Detrusor underactivity
Underactive bladder
Detrusor failure
Chronic urinary retention

Abstract

Context: Detrusor underactivity (DU) is a common cause of lower urinary tract symptoms (LUTS) in both men and women, yet is poorly understood and underresearched.
Objective: To review the current terminology, definitions, and diagnostic criteria in use, along with the epidemiology and aetiology of DU, as a basis for building a consensus on the standardisation of current concepts.
Evidence acquisition: The Medline and Embase databases were searched for original articles and reviews in the English language pertaining to DU. Search terms included *underactive bladder, detrusor underactivity, impaired detrusor contractility, acontractile detrusor, detrusor failure, detrusor areflexia, raised PVR* [postvoid residual], and *urinary retention*. Selected studies were assessed for content relating to DU.
Evidence synthesis: A wide range of terminology is applied in contemporary usage. The only term defined by the standardisation document of the International Continence Society (ICS) in 2002 was the urodynamic term *detrusor underactivity* along with *detrusor acontractility*. The ICS definition provides a framework, considering the urodynamic abnormality of contraction and how this affects voiding; however, this is necessarily limited. DU is present in 9–48% of men and 12–45% of older women undergoing urodynamic evaluation for non-neurogenic LUTS. Multiple aetiologies are implicated, affecting myogenic function and neural control mechanisms, as well as the efferent and afferent innervations. Diagnostic criteria are based on urodynamic approximations relating to bladder contractility such as maximum flow rate and detrusor pressure at maximum flow. Other estimates rely on mathematical formulas to calculate isovolumetric contractility indexes or urodynamic "stop tests." Most methods have major disadvantages or are as yet poorly validated. Contraction strength is only one aspect of bladder voiding function. The others are the speed and persistence of the contraction.
Conclusions: The term *detrusor underactivity* and its associated symptoms and signs remain surrounded by ambiguity and confusion with a lack of accepted terminology, definition, and diagnostic methods and criteria. There is a need to reach a consensus on these aspects to allow standardisation of the literature and the development of optimal management approaches.

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0302-2838/$ – see back matter © 2013 Published by Elsevier B.V. on behalf of European Association of Urology.
http://dx.doi.org/10.1016/j.eururo.2013.10.015

1. Introduction

Detrusor underactivity (DU) is a common lower urinary tract dysfunction that is poorly understood and under-researched. Although the International Continence Society (ICS) has defined DU [1], many other terms are used to describe this entity with a variety of definitions in the contemporary literature. The clinical features of impaired bladder emptying (eg, reduced urinary flow rate, raised postvoid residual [PVR]) may arise as a result of DU but may also occur due to bladder outflow obstruction (BOO) (eg, benign prostatic enlargement, urethral stricture). As such it is often difficult to distinguish DU and BOO without invasive pressure flow studies.

In stark contrast to detrusor overactivity (DO) and overactive bladder (OAB) syndrome, DU has received scant attention in the clinical and scientific literature due to a lack of unified terminology, detailed definitions, and accepted diagnostic criteria with the exception of a reduced voiding pressure with failure of the bladder to empty efficiently during a urodynamic pressure-flow study (PFS). Moreover, there is a lack of even basic insights into the underlying aetiopathogenesis, and the absence of efficacious therapies has led to the common perception amongst clinicians that DU with its resultant symptoms is an incurable problem.

This review focuses on the impairment of bladder emptying function due to the inability of the detrusor to contract effectively rather than on BOO. The literature pertaining to terminology, definitions, epidemiology, aetiology, and diagnostic methods in DU is evaluated to help facilitate future consensus building and standardisation.

2. Evidence acquisition

The Medline and Embase databases were searched for reports in English pertaining to DU from 1 January 1950 to 1 January 2013. A wide set of search terms was used including *underactive bladder, detrusor underactivity, bladder underactivity, impaired detrusor contractility, acontractile detrusor, detrusor failure, hypotonic bladder, detrusor areflexia, raised PVR*, and *urinary retention*. Abstracts were screened for relevance to DU and in terms of prevalence data in clinical series of patients undergoing urodynamic evaluation. Original studies, review articles, commentaries, and editorials were included. The full texts of selected studies were assessed for content relating to definitions, terminology, epidemiology, aetiology, and diagnostic methods.

3. Evidence synthesis

3.1. Terminology

There is a lack of high-level evidence relating to terminology in the assessment of detrusor voiding function. Consequently, the validity of the current terms is reviewed and evaluated largely on the basis of logical reasoning and expert opinion.

A variety of terms have been used to describe the nonobstructive impairment of voiding function, referred to here as DU in accordance with ICS terminology and recent recommendations [2]. Other terms used include *impaired detrusor contractility* [3], *underactive bladder* [4], as well as older terms such as *detrusor areflexia* [5], *hypotonic bladder* [6], and *detrusor failure* or *bladder failure* [7]. Although it is agreed that the diagnosis of DU is primarily urodynamic, the plethora of terms reflects a general ambiguity and lack of consensus.

Impaired detrusor contractility, one of the most commonly used terms, implies a deficiency in the contractile properties of the detrusor. This term is inappropriate in several respects. First, a PFS provides only a proxy measure for contractility based on the pressure generated within the bladder to allow flow through a patent bladder outlet. A true change in muscle contractility is defined as altered isometric contraction tension, independent of resting muscle length [8], measured directly using muscle strips. A urodynamic evaluation clearly does not identify which of the individual contributory components (ie, the detrusor muscle or its innervation) is impaired. Impaired detrusor contractility implies a reduction in contraction strength when in fact the problem may be that of a reduced speed or persistence of contraction.

Terms such as *detrusor failure* or *bladder failure* give the impression of an all-or-nothing event, whereas empirical clinical evidence would suggest a continuum of activity and so would not apply to those patients with symptoms and preserved bladder emptying, albeit with underactive detrusor function. Similarly, *detrusor areflexia* as a term reflects the older nomenclature that is the converse of detrusor hyperreflexia, which from a semantic perspective is inappropriate in contemporary usage. The term *hypotonic bladder* also implies a reduction in detrusor tone, a sustained state of contraction that occurs during filling and so is not strictly specific to the voiding phase of bladder function.

DU (or a potential alternative, bladder underactivity) has the advantage of a published urodynamic definition that relates to the abnormalities underlying symptoms. The equivalent in terms of symptoms could be *underactive bladder* (compare DO as the urodynamic term and OAB as the symptom complex). However, the term *underactive bladder*, by virtue of the vagueness of its clinical characterisation based on symptoms, is unlikely to mean as much to patients and clinicians as OAB.

3.2. Definitions

The 2002 ICS standardisation report defines DU as "a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span" [1]. This definition is hampered by the subjective interpretation of what constitutes reduced strength, reduced length of contraction, or prolonged emptying. Nevertheless, the definition provides a useful conceptual framework within which to define the functional abnormality underlying the clinical presentation of patients who may have variable symptoms because it is recognised that the "bladder is an unreliable witness" [9]. Certainly symptoms, particularly in the context of DU, are poorly correlated with the underlying aetiology. The contribution of a slow shortening velocity is also potentially important and should be incorporated into any definition [10].

The ICS defines an "acontractile detrusor" (AcD) as one where no detrusor contraction whatsoever is generated. This is distinct from the inability to void during a PFS, which is a common occurrence, and the two can usually be differentiated on the basis of the clinical history. The logical assumption is that DU represents a spectrum of which AcD is an extreme, although temporal factors need to be considered in determining if this is the case or whether AcD is the terminal consequence of a progressive pathophysiologic condition.

The ICS does not classify DU based on probable underlying aetiology (eg, neurogenic or idiopathic) as is the case for DO. Such a classification may better facilitate the study of the problem and future research [2]. A further deficiency is arguably the failure to include a definition based on symptoms that could potentially describe a clinical syndrome of "underactive bladder" (UAB), thereby mirroring the scenario of OAB. This could follow along the lines of a statement such as "reduced sensation of the need to void (the opposite of urgency) that may be associated with frequency and nocturia or reduced voiding frequency often with a feeling of incomplete bladder emptying and incontinence that may predominate at nighttime." The advantage of such an approach is the focus on symptoms that patients find bothersome as well as the potential to raise the profile of this important clinical condition and thereby focus research efforts [11]. It is clearly problematic, however, because the symptoms of UAB and the underlying detrusor abnormality have not been correlated in any prospective study. By contrast, OAB is far simpler to rationalise based on the sensation of urgency, albeit variably correlated with an underlying urodynamic abnormality [12].

Further complicating the development of a definition of UAB on which treatment could be based (as in OAB) are the multiple factors that need to be considered: the presence or absence of sensation of incomplete bladder emptying; the degree of urodynamic DU, in particular the strength and persistence of the detrusor contraction; the extent to which the bladder is able to empty; and the degree of outlet resistance that means incontinence is less common in men (just as with OAB), until a later stage in chronic retention when nocturnal incontinence develops. This is a much more complex situation as contrasted with OAB, where the initial management approach is well defined regardless of whether DO is subsequently confirmed or not.

If UAB is to be considered a symptom syndrome, a potential indicator of significantly underactive detrusor function could be a raised PVR $\geq$40% of the bladder capacity (volume voided plus PVR). Many would agree this is significantly abnormal; however, there remains a lack of consensus on this point.

3.3. *Clinicoepidemiology*

Lower urinary tract symptoms (LUTS) are a major global health issue that show an age-related increase in prevalence, yet the extent of the contribution of DU as an underlying mechanism remains unknown. To date no epidemiological work has been able to evaluate this separately, with the main focus on the prevalence of storage, voiding, and postmicturition LUTS, with an inference that storage LUTS are a proxy for OAB. The fundamental problem is that DU is a urodynamic diagnosis, rendering the interpretation of epidemiologic data difficult and limiting our knowledge of the incidence, prevalence, risk factors, and natural history of the condition.

The clinical features that result from DU are often indistinguishable from other lower urinary tract dysfunctions, in particular hesitancy, weak stream, intermittency, and straining that are all common symptoms seen in patients with BOO. Urinary flow rate is used as a screening test for BOO but does not distinguish between BOO and DU [13]. A raised PVR and urinary retention may both result from DU but also may occur due to BOO [14]. *Urinary retention* is a nonspecific term whose definition, based on PVR as noted earlier, remains the subject of controversy and especially in men is considered a product of variable degrees of BOO and/or DU. Chronic urinary retention (CUR) was traditionally defined as a PVR >300 ml, whereas the recent ICS report avoids committing to an absolute volume, stating it is "a non-painful bladder, which remains palpable or percussable after the patient has passed urine" [1]. Conversely, in OAB as a consequence of frequency with reduced voided volumes, voiding symptoms may also be prevalent, and can also be seen in the elderly with the condition of detrusor hyperreflexia with impaired contractility (DHIC) [15]. In the male population most of the research has focused on benign prostatic enlargement leading to BOO as the cause of voiding LUTS, retention, and raised PVR, although it is estimated that 10–20% of patients with low flow at presentation have an element of DU [16]. The relationship between BOO and DU is incompletely understood. It is certainly the case that not all men with BOO develop DU, and similarly not all men with DU have coexistent BOO [17]. It is probable that BOO is a cause of DU in some men, whereby contractile function of the detrusor is impaired due to the structural and neurophysiologic consequences of prolonged BOO. In others, DU may represent an entirely independent disease process, as has been postulated for those men developing CUR that is usually asymptomatic until a late stage and indeed may present for the first time with nocturnal enuresis.

Although in men it is difficult to determine the contributions of BOO and DU as the underlying cause of LUTS, retention, or raised PVR on a population basis, in women BOO is far less common, occurring in 2.7% of those referred for urodynamic studies from a general population [18]. Thus retention and raised PVR in women are far more likely to represent DU. Most causes of BOO in women are iatrogenic, most commonly after incontinence surgery. Other anatomic obstructions include pelvic organ prolapse, urethral stricture, urethral diverticula, and large fibroids. Alternatively, BOO may occur due to functional causes such as Fowler's syndrome [19].

Clinical studies of patients with non-neurogenic LUTS referred for PFS (Table 1) suggest that DU is present in 9–28% of men <50 yr of age increasing to as much as 48% in men >70 yr. In older women, prevalence ranges from 12% to 45%, peaking in those who are institutionalised where DHIC is an important cause of incontinence. Such retrospective series reliant on post hoc interpretation of urodynamic data clearly have inherent limitations [20], and considering the wide variations in definitions used as primary outcome measures, the results cannot be extrapolated to the general population. However, the results do demonstrate that DU is sufficiently common in the group of patients seen in secondary care to warrant careful consideration.

A study by Thomas et al. [17] of a 10-yr follow-up of men diagnosed with DU (maximum flow rate [Q_{max}] <15 ml/s, $P_{det}@Q_{max}$] <40 cm H_2O) and initially managed with watchful waiting (no catheterisation) provides insights into the possible natural history of DU. Sixty-nine men who initially opted for watchful waiting were followed up with urodynamic studies (mean follow-up: 13.6 yr). There was no significant deterioration in symptomatic or urodynamic parameters over time. Only 11 patients failed the initial watchful waiting and underwent transurethral resection of the prostate, 8 (11.6%) due to worsening LUTS and 3 (4.35%) due to acute retention. Those with worsening LUTS had repeat flow studies preoperatively that showed no significant change compared with baseline values. The main conclusion from this study is that DU is not progressive in most non-neurogenic male patients, and an initial conservative approach may be justified. Interestingly, the mean PVR of 108–126 ml at the end of the 10-yr follow-up suggests that DU often does not result in CUR in this group. Further studies are required before any definitive conclusions can be drawn.

3.4. *Aetiology*

The presence of DU in diverse clinical groups suggests a multifactorial aetiopathogenesis (Table 2) [33], rather than occurrence solely as a function of normal ageing. Current theories are based on bridging knowledge from in vivo and in vitro investigations, in both animal and humans, with clinical evidence.

A myogenic basis for DU may represent any abnormality of the intrinsic propensity of the myocytes to generate contractile activity in the absence of external stimuli [34], or alternatively the problem may lie with the extracellular matrix. The ultrastructural changes accompanying normal ageing were described by Elbadawi et al., who also characterised the patterns occurring in other LUT dysfunctions [35–37]. DU was typified by changes including widespread detrusor myocyte disruption and axonal degeneration [35], which correlated well with impaired contractility, defined as a PVR >50 ml [38]. It is not clear whether these changes represent a cause or an effect of factors resulting in DU or they are unrelated. The disruption to detrusor myocytes could account for impairments in cell

Table 1 – Prevalence of detrusor underactivity in a clinical series of patients with nonneurogenic lower urinary tract symptoms undergoing urodynamic studies

Study	Population	Size	Age range, yr	Diagnostic criteria	Prevalence of DU, % (% of acontractile detrusors)
Fusco et al. [21]	Male	541	26–89	$P_{det}@Q_{max} \leq 30$ and $Q_{max} \leq 12$	10
Kuo [22]	Male	1407	46–96	Relaxed sphincter EMG with open membranous urethra during voiding and low flow rate	10.6
Nitti et al. [23]	Male	85	18–45	Bladder outlet obstruction index <20 and uroflow <12 ml/s	9
Wang et al. [24]	Male	90	18–50	$P_{det}@Q_{max}$ <30, Q_{max}<15	10
Kaplan et al. [25]	Male	137	18–50	$P_{det}@Q_{max}$ <45 cm and Q_{max}<12 ml	23 (5)
Karami et al. [26]	Male	456	18–40	ICS definition	12.9 (10.5)
Arbabanel et al. [27]	Male	82	>70	$P_{det}@Q_{max}$ <30 cm H_2O and Q_{max} <10 ml	48
	Female	99	>70		12
Jeong et al. [28]	Male	632	>65	Bladder Contractility Index <100 (men)	40.2
	Female	547	>65	$Q_{max} \leq 12$, $P_{det}@Q_{max} \leq 10$ (women)	13.3
Resnick et al. [29]	Male	17	87	In the absence of obstruction, Underactive detrusor: "Failure to empty in the absence of an increase abdominal pressure." DHIC: "Involuntary detrusor contraction that emptied less than half of volume instilled"	41.2
	Female (institutionalised)	77			37.7
Resnick et al. [30]	Female (institutionalised)	97	87.6*	"Reproducible failure of the involuntary contraction to empty at least half of bladder contents in the absence of straining, urethral obstruction, and detrusor-sphincter dyssynergia"	45*
Groutz et al. [31]	Female	206	62.6 ± 15.8 yr†	ICS definition	19
Valentini et al. [32]	Female	442	>55	"Impaired detrusor contraction leading to prolonged voiding time and high residual volume"	13.8

DHIC = detrusor hyperreflexia with impaired contractility; DU = detrusor underactivity; EMG = electromyogram; ICS = International Continence Society; $P_{det}@Q_{max}$ = detrusor pressure at the time of maximum flow; Q_{max} = maximum flow rate.
* DHIC.
† Mean plus or minus the standard deviation.

Table 2 – Aetiological factors leading to detrusor underactivity

Type	Possible causes
Idiopathic	Normal ageing*
	Unknown cause in younger population*
Neurogenic	Parkinson disease
	Multisystem atrophy
	Diabetes
	Multiple sclerosis
	Guillain-Barré syndrome
	Spinal-lumbar disc hernia/spinal cord injury/congenital
Myogenic	Bladder outlet obstruction*
	Diabetes*
Iatrogenic	Pelvic surgery
	Radical prostatectomy
	Radical hysterectomy
	Anterior resection, abdominoperineal resection

* Likely major aetiological factors.

contractile properties by affecting ion storage/exchange, excitation-contraction coupling mechanisms, calcium storage, and energy generation, so that even in the presence of normal extrinsic neuronal activity, a reduced contraction may still result [39]. A similar pattern was observed in a subset of patient with BOO and large PVR (>150 ml) [40]. The mechanisms of BOO-related DU have been well studied in numerous animal models where sequential changes were described leading to decompensation of detrusor function [41]. Long term untreated BOO does not appear to result in significant clinical decompensation of detrusor function in most men, highlighting the limitations in extrapolating animal data to the human situation [42].

Dysfunction of the central neural control of the voiding reflex may lead to DU by impacting upon key processes in perception, integration, and outflow [33]. Functional imaging has provided many insights. Studies in the rat and cat [43–45] showed that some populations of pontine micturition center (PMC) neurons, termed *direct neurons*, fire just before and during reflex bladder contractions, being inactive outside these periods, and a large proportion of these neurons pass to the lumbosacral spinal cord. Functional neuroimaging in humans suggests that similar areas in the brainstem and cortex are involved in the voiding reflex, namely the insula, the hypothalamus, the periaqueductal grey, and the PMC [46].

Disruption to the efferent nerves may result in reduced neuromuscular activation that may manifest as an absent or poor detrusor contraction. This is typically seen with diseases causing direct neuronal injury such as multisystem atrophy and other autonomic neuropathies. In DU of non-neurogenic origin, the exact contribution of efferent dysfunction is unknown. The decline in autonomic nerve innervation in normal human bladders with ageing [47], as well as BOO [48], may contribute to insufficient activation for adequate contraction to occur in individuals without overt neurologic disease [33].

The afferent system is integral to the function of the efferent system in the neural control of micturition during both the storage and voiding phases. The afferent system monitors the volumes during storage and also the magnitude of detrusor contractions during voiding. Urethral afferents respond to flow and are important in potentiating the detrusor contraction [49,50]. Bladder and urethral afferent dysfunction may lead to DU by reducing or prematurely ending the micturition reflex, which may manifest in a loss of voiding efficiency [33], as is the case in diabetic cystopathy.

3.5. *Diagnosis*

An invasive PFS is currently the only definitive method of measuring detrusor contractile function. There is a wide variation in the urodynamic criteria considered as diagnostic of DU in clinical studies reported, from which two aspects are worthy of comment: (1) Most measures only assess detrusor contraction strength (as opposed to sustainability or speed of contraction), and (2) estimation of strength is based on the Q_{max} and $P_{det}@Q_{max}$. For both of these, threshold values are set around the lower limits of the normal range, which for men are derived from a historical series of patients undergoing bladder outlet surgery [14,51]. Because these ranges may not be applicable to all groups, some authors have studied healthy (young) men [52,53] and women [54], although these studies are limited in number.

The urodynamic estimation of detrusor contractile function is based on the detrusor pressure required to expel urine through a patent urethra and is likely to underestimate contractility because the contraction generates both flow and pressure [55]. To compensate, methods attempting to estimate isovolumetric detrusor pressure during uninterrupted or interrupted voiding were developed [56]. Some of these are rather confusing, which is presumably the reason for their limited use in clinical studies. Most have their basis in the bladder outlet relation (BOR) [57], the inverse relation between pressure and flow, which is equivalent to the Hill equation for actively contracting muscle [58]. The BOR can be summarised as follows: In any given bladder if outflow is stopped, the detrusor pressure reaches its highest possible value (isovolumetric pressure); when increasing flow is allowed, pressure decreases and reaches a minimum when flow reaches a maximum. On this basis, measuring detrusor pressure at the time of highest flow (ie, $P_{det}@Q_{max}$) does not correlate to the peak of contraction strength. Methods that assess isovolumetric detrusor pressure are either based on a post hoc mathematical analysis of urodynamic data or real-time interruption of flow (Table 3).

Another measure of detrusor function, the watts factor (WF), estimates the power per unit area of bladder surface generated by the detrusor, corrected for the finite power required for either isometric contraction or for shortening against no load. This is represented by the following formula where V_{det} represents detrusor shortening velocity and a and b are fixed constants ($a = 25$ cm H_2O; $b = 6$ mm/s), obtained from experimental and clinical studies [59]:

$$WF = [(P_{det} + a)(V_{det} + b) - ab]/2\pi$$

Table 3 – Summary of diagnostic methods

Type	Method	Advantages	Limitations
Mathematical calculations	Watts factor	1. Measure of bladder power 2. Minimally dependant on volume of urine 3. Not affected by presence of BOO	1. Lengthy and complex calculation 2. No validated thresholds 3. Does not measure sustainability of contraction
	Detrusor shortening velocity	May identify early stage DU	
Indexes	Detrusor contraction coefficient	1. Simple to use 2. Measurement easy to obtain 3. Estimation of isovolumetric contraction	1. Does not measure sustainability of contraction 2. May not be applicable to other groups 3. Does not conceptually consider coexistence of BOO and DU
	Bladder Contractility Index		
Occlusion testing	Voluntary stop test	1. Real-time indication of isovolumetric contraction strength 2. No calculations	1. Uncomfortable or painful for patients 2. Impractical 3. No information on sustainability of contraction in (continuous occlusion) 4. May underestimate isovolumetric pressure (stop test) 5. Unusable in some patient groups
	Mechanical stop test		
	Continuous occlusion		
Ranges of urodynamic measurements	$P_{det}@Q_{max}$ (eg, <40) Q_{max} (eg, <15)	Simple to use	1. No widely accepted "normal" ranges 2. Underestimates contraction strength 3. Does not conceptually consider coexistence of BOO and DU

BOO = bladder outlet obstruction; DU = detrusor underactivity; $P_{det}@Q_{max}$ = detrusor pressure at the time of maximum flow; Q_{max} = maximum flow rate.

Because P_{det} and V_{det} vary through the voiding cycle, the WF also varies. Two points have been proposed as the most representative of detrusor contractility: the maximum WF (WF_{max}) [60] and the WF at maximum flow (Wq_{max}). The advantages of the WF are that it depends minimally on bladder volume [59] and is not affected by the presence of BOO [61]. However, it does not provide a measure of contraction sustainability and involves a complex calculation, limiting its use in clinical practice. There are also no validated threshold values of normality, although experts have suggested 7 W/m^2 [2].

Schafer proposed a simpler method to assess detrusor contraction strength by drawing the linear passive urethral resistance relation (linPURR) onto Schafer's pressure/flow nomogram whereby the peak of the PURR signifies the detrusor contraction strength [62]. The maximum isovolumetric pressure can be estimated using the point Pdet/Q_{max}, if the angle and curvature of the BOR are known. To do this, the BOR is simplified to a straight line with a fixed angle (K) taken as 5 cm H_2O/ml per second (male benign prostatic hyperplasia [BPH] population). The isovolumetric pressure is then estimated by projecting back to the y-axis (P_{det}) in a line parallel to the BOR represented by this formula (projected isovolumetric pressure [PIP]) [63]:

$$PIP = P_{det}@Q_{max} + 5Q_{max}$$

Threshold values for contraction strength were suggested, with >150 representing strong contraction; 100–150, normal contraction; 50–100, weak contraction; and <50, very weak contraction. By drawing the corresponding BORs on the pressure flow plot, a contractility nomogram was developed. Because PIP >100 cm H_2O represents normal contraction strength, the actual PIP divided by 100 gives a coefficient, termed the *detrusor coefficient* (DECO), whereby a value <1 signifies weak contraction.

Abrams described the Bladder Contractility index (BCI) based on the PIP formula that divides contractility into three groups (strong >150, normal 100–150, and weak <100); in principle this is the same as DECO [64]. In common with the WF, these methods do not measure the sustainability of contractions. Additionally, the fixed angle K needs adjusting to the particular group studied. Whereas a value of 5 cm H_2O/ml per second is suitable for men with BPH, it is unlikely to be applicable in other groups. An angle of 1 cm H_2O/ml per second was found to be more accurate in older women [56]. The BCI may have clinical utility. It is simple and quick to calculate and easily reproducible, but it is problematic because it does not consider conceptually the coexistence of DU and BOO.

By using voluntary or mechanical interruption of the urine flow, an estimation of isovolumetric detrusor pressure ($P_{det,iso}$) can be obtained [65]. In voluntary "stop tests," the patient is asked to interrupt the flow midstream by contracting the external urethral sphincter, whereas mechanical interruption involves blocking the urethra (eg, by pulling a catheter balloon against the bladder neck during midstream). A continuous occlusion test has been described where the outflow is occluded before the onset of detrusor contraction. The three techniques show good correlation with each other in both men [66] and women [67]. However, the voluntary stop test gives a $P_{det,iso}$ approximately 20% less than the other two [66]. This may occur due to a reflex inhibitory effect on the detrusor due to external sphincter contraction. Voluntary stop tests are not possible in some patients, especially in the frail or those with neurologic dysfunction or stress incontinence.

Continuous occlusion has a better test-retest reliability than mechanical stop tests, possibly due to the degree of discomfort associated with the latter, and it has the advantage of allowing an assessment of sustainability of isometric contraction. It also correlates well with bladder voiding efficiency [68]. However, continuous occlusion is problematic because it does not allow the measurement of flow, may be painful, and is highly impractical in routine clinical practice.

Noninvasive techniques assessing contraction strength have been explored but have not replaced standard PFS in clinical practice. McIntosh et al. used an inflatable penile cuff to interrupt voiding, finding this method to overestimate $P_{det,iso}$ by 16.4 cm H_2O, attributed to the positioning of the cuff below the bladder [69]. Patients understandably found cuff assessment more acceptable than invasive PFS; however, the test was limited by frequent failure and variability of agreement. Another technique is to use condom catheters where a continuous column of fluid from the catheter via condom to the urethra and bladder allows measurement of pressure. Measurements of $P_{det,iso}$ correlate well with invasive PFS in nonobstructed patients but less so in BOO [70]. Several problems can lead to artefacts such as leakage around the condom, closure of the external sphincter in response to line occlusion, and increased compliance within the system [71]. Common problems of both techniques are lack of appreciation of abdominal straining and pressure transmission capture.

From the WF equation it can be seen that WF is the product of P_{det} and V_{det}. Therefore, conceptually, a low WF could result from a reduced V_{det} and a normal P_{det}. As such patients with DU could have bladders that are slow and weak, but some may solely have slow bladders. In a series of longitudinal studies in both men [10,72] and women [73] with idiopathic DU, a reduction in V_{det} preceded the reduction in P_{det}, suggesting a two-stage process in the development in DU. Shortening velocity was calculated using the following equation where Q represents the flow rate (millilitres per second), V represents bladder volume (millilitres), and Vt represents the volume of noncontracting bladder wall tissue:

$$V_{det} = Q/2[3/(V + Vt)/4\pi]^{0.66}$$

On the basis of these studies, Cucchi et al. proposed a new definition of DU incorporating contraction speed: “slower and/or weaker bladder with or without poorly sustained micturition contractions” [74].

Ambulatory PFS may have a role in in the diagnosis of DU when detrusor acontractility is demonstrated in conventional PFS. A study by van Koeveringe et al. found that in 71% of patients in whom no detrusor contraction was demonstrable on conventional PFS, there was obvious contractility in ambulatory studies [75]. The probable explanation is that during PFS patient anxiety leads to pelvic floor/sphincter contraction that triggers the guarding reflex, impairing detrusor contraction [76]. Furthermore, a conventional PFS is conducted at nonphysiologic filling rates, and so its validity as a modality for assessing detrusor contractility can be questioned. Conversely, ambulatory PFS remains a nonstandardised urodynamic technique.

Given the importance of an intact afferent system to bladder voiding function, evaluation of bladder sensation is an important aspect of the urodynamic assessment of patients with impaired bladder emptying. It is most commonly undertaken by asking the patient to report the first sensation of bladder filling during filling cystometry, followed by the first desire to void and the strong desire. Normal values in healthy volunteers have been published [77]. Delayed bladder sensation is taken to signify impaired sensory function, although this method has been criticised as subjective and crude because some patients report a sensation of bladder filling even when the bladder is not being filled [78,79]. Attempts at a more objective quantification have been made using electrical sensation testing utilising the passage of sine or square wave electrical current through the bladder wall to determine the current perception threshold (CPT). Studies comparing volume and/or pressure at filling sensation to CPT are few but have often shown no correlation between the two [80–82]. CPT testing has been criticised because electrostimulation is not a normal physiologic stimulus, and the clinical utility of the technique remains to be established.

4. Conclusions

It is apparent that the lower urinary tract dysfunction described in this article as DU is surrounded by ambiguity. In terms of terminology, DU, as adopted by the ICS, has the advantage of a recognised definition but may be restrictive in that it focuses on dysfunction of the detrusor muscle, whereas the underlying pathophysiologic abnormality may be a bladder afferent problem. UAB, the antithesis of OAB, has clear attractions as a concept but may be problematical to introduce because it is a complex series of symptoms that vary from patient to patient and requires at the very least measurement of PVR. It is clear there is no easily identifiable index patient because a number of aetiologies lead to DU. Such aetiologies may have an impact on the ability of the detrusor to contract efficiently by affecting the muscle itself (myocytes and/or extracellular matrix), the efferent and afferent nerves, or the central neural control of micturition.

Application of the ICS definition is hampered by the fact that what constitutes reduced contraction strength or length and prolonged voiding are currently not definable. Any attempts at redefinition should address this dilemma, as well as exploring whether contraction speed or symptoms should be included. DU is impossible to differentiate from BOO on the basis of symptoms, urinary flow rate, or raised PVR, making large studies on epidemiology and natural history difficult. Current methods of diagnosis rely on invasive PFS and have methodological limitations. Accurate noninvasive methods of estimating bladder contraction that would allow the acquisition of larger data sets are needed.

Author contributions: Nadir I. Osman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Osman, Chapple.
Acquisition of data: Osman, Chapple.
Analysis and interpretation of data: Osman, Chapple.
Drafting of the manuscript: Osman, Chapple.
Critical revision of the manuscript for important intellectual content: Osman, Chapple, Abrams, Dmochowski, Haab, Nitti, Koelbl, van Kerrebroeck, Wein.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: None.
Other (specify): None.

Financial disclosures: Nadir I. Osman certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Nadir I. Osman has nothing to disclose. Christopher Chapple is a consultant and researcher for Astellas, Pfizer, Recordati, Allergan, and Lilley. Paul Abrams is a consultant for Astellas, Allergan, Merck, Ipsen, ONO, a lecturer for Pfizer, Astellas, and Ferring, and an investigator for Astellas. Roger Dmochowski is a consultant for Allergan and Medtronic. François Haab is a consultant and lecturer for Astellas, Allergan, Pfizer, Helsinn, and Sanofi. Victor Nitti is a consultant for Allergan, Astellas, Medtronic, Ono, Pfizer, and Serenity. He is an investigator and speaker for Allergan and an investigator for Astellas. Heinz Koelbl is on the Astellas International Advisory Board and the Allergan International Advisory Board. Philip van Kerrebroeck is an adviser to Astellas, Allergan, and Ferring. Alan Wein is an adviser/consultant to Astellas, ONO, Pfizer, Medtronic, OPKO, AltheRx, Ferring, and Allergan.

Funding/Support and role of the sponsor: None.

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Neurourology and Urodynamics

Detrusor Underactivity: Pathophysiological Considerations, Models and Proposals for Future Research. ICI-RS 2013

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Aims: Detrusor underactivity, resulting in either prolonged or inefficient voiding, is a common clinical problem for which treatment options are currently limited. The aim of this report is to summarize current understanding of the clinical observation and its underlying pathophysiological entities. **Methods:** This report results from presentations and subsequent discussion at the International Consultation on Incontinence Research Society (ICI-RS) in Bristol, 2013. **Results and Conclusions:** The recommendations made by the ICI-RS panel include: Development of study tools based on a system's pathophysiological approach, correlation of in vitro and in vivo data in experimental animals and humans, and development of more comprehensive translational animal models. In addition, there is a need for longitudinal patient data to define risk groups and for the development of screening tools. In the near-future these recommendations should lead to a better understanding of detrusor underactivity and its pathophysiological background. *Neurourol. Urodynam.* © 2014 Wiley Periodicals, Inc.

Key words: ageing; detrusor underactivity; experimental animal models; lower urinary tract symptoms; underactive bladder; urinary tract physiology; voiding dysfunction

INTRODUCTION

Detrusor underactivity has been defined by the International Continence Society as as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span.[1] Successful and complete emptying is necessarily determined by the interplay of several factors including the ability of the bladder to empty, and the resistance offered by the outflow tract (i.e., the capacity of outlet opening). Diminished bladder emptying may occur because of reduced detrusor contractile ability (not equivalent to contractility), an impairment of the outflow tract or a combination of these factors. To a certain extent, both factors may be able to compensate for each other but this compensatory capacity may change in association with disease and ageing.

Anatomical (structural) or physiological (functional) changes may impair either detrusor contractile ability or urethral opening capacity. Efferent nerves may be damaged; the amount of muscle in the bladder wall reduced or replaced by connective tissue, or there may be a reduction in true contractility. In addition, structural bladder outlet obstruction can reduce effective voiding. When both bladder contractile function and the bladder outlet are adequate, an impairment of sensory nerves may also lead to inefficient voiding.

To void efficiently, a feed-forward mechanism by which urinary flow in the urethra helps to enhance and maintain adequate contractile function of the bladder, until the bladder is empty is required. Sensory information is fed back to the motor system at several levels of control between the end organ and brain cortex. These sensors themselves can be damaged, for example through an effect of ageing or ischaemia. In addition, impairment of innervation can lead to decreased information transfer via either the sensory or motor nerves. A functional disruption of higher central nervous regulatory systems can lead to functional abnormal voiding. This can occur as a result of disease induced deregulation (e.g., Parkinson's or Alzheimer's disease), ageing induced defects and psychological or psychiatric pathology.

Whether ageing related defects in these systems lead to inefficient emptying depends on the compensatory ability of mechanisms involved in voiding. To manage a dysfunction, the defect itself may be treated, but the compensatory capacity of another mechanism can also be improved. The choice of treatment may depend on the therapeutic effect required and the potential side-effects of the proposed treatment.

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Christopher Chapple led the peer-review process as the Associate Editor responsible for the paper.
Conflict of interest: none.
Grant sponsor: National Institute of Neurological Disorders and Stroke; Grant number: R01NS070267
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Received 10 December 2013; Accepted 20 February 2014
Published online in Wiley Online Library
(wileyonlinelibrary.com).
DOI 10.1002/nau.22590

The most comprehensive approach to diagnose and treat voiding inefficiency in humans is first to study the pathophysiological alterations leading to impaired bladder emptying in humans. Animal models that mimic elements of derangements, as discussed above may be helpful to identify options that ameliorate these defects, or stimulate compensatory mechanisms and so define potentially treatable options in humans.

Since publication of the ICI-RS article in 2011 the topic of detrusor underactivity (DU) has received increasing research interest,[2] with 54 articles retrievable by PubMed using DU/underactive bladder as search terms. However, few of these publications lead to better understanding of the complex pathophysiology underlying this urological entity.[3–7] There are still many uncertainties with regard to the underactive bladder, particularly the role of ageing, altered sensory function, and the translational value of existing animal models.

AGEING: THE PRIMARY CAUSE OR A CONDITION NECESSARY FOR DEVELOPMENT OF DETRUSOR UNDERACTIVITY?

The prevalence of impaired bladder emptying is associated with increasing age and occurs in both men and women.[8–10] This is manifest in the frequent finding of a raised post-void residual urinary volume in an otherwise asymptomatic older person[11] and in association with other lower urinary tract diagnoses upon presentation to a clinician.[12] Impaired bladder emptying has most often been described in association with detrusor overactivity, regardless of the presence of bladder outlet obstruction.[13] Urodynamic data revealing impaired emptying function in the elderly are conflicting,[14] and also are limited to those with symptoms, perhaps limiting the interpretation of age-associated pathophysiology. Histologically, older bladders differ from those in younger people, in that there is an age-associated accumulation of connective tissue and collagen, resulting in a reduction of the smooth muscle: collagen ratio,[15] which may lead to a reduction of transmitted contractile force. At the level of the muscle cell, detrusor contractility is not reduced with ageing in those without detrusor overactivity or obstruction, unlike the diminution reported in older people with these conditions.[16] The reduction of bladder sensory function reported in association with increasing age[17] may also contribute to DU. Functional magnetic resonance imaging in asymptomatic older people found diminished response to bladder filling in the insula, an area of the brain responsible for mapping visceral sensations.[18] The current state of the limited evidence suggests that a number of factors associated with ageing may, per se, predispose to impaired emptying and that it is likely that, for those unaffected older people, their compensatory capacity outweighs the drivers of impaired emptying.

THE ROLE OF ALTERED SENSORY FUNCTION IN DETRUSOR UNDERACTIVITY

Impaired bladder contractile ability has been traditionally regarded as a major aetiological factor of DU. However, in the elderly, decreased bladder sensations are associated with DU and suggest a more complex pathology. Because detrusor contraction force and duration are a result of efferent nerve activity in combination with an adequate contractile ability, which in turn is dependent on sensory input, there is the potential for impaired afferent function to cause DU.[19] Structural and functional tissue changes accompanying ageing and particular diseases may result in altered bladder afferent function, with subsequent reflex impairment of voiding function.

The urothelium, detrusor muscle, interposed interstitial cells, and ganglia collectively form a mechano-sensitive sensor-transducer system which activates afferent nerve fibres.[19] Abnormalities in each of these components could have an impact on LUT function by altering release of neurotransmitters, as well as the excitability of sensory fibres and the contractility of detrusor muscle in the urinary bladder. Furthermore, because many urothelial functions may be altered with age, defects in urothelial cells may contribute to age-related changes. Moreover, positive sensory feedback from urethral afferents, in response to flow, has been shown to augment detrusor pressure amplitude and duration, and is necessary for efficient voiding,[20] thus urethral sensory disturbance could also lead to DU in specific patient categories.

In addition to the positive feedback mechanism described above, a defect in sensory function of the bladder itself may lead to delayed voiding and overdistention, again leading to damage of the sensors, denervation, or impaired muscle function.

WHAT IS THE VALUE OF CURRENT ANIMAL MODELS OF CONCOMITANT DISEASE?

The reason for developing animal models is usually to mimic part of a human pathology or a functional problem. Since the clinical problems in DU are in the voiding phase and involve "prolonged duration" and/or "reduced contractile strength," it is worthwhile to concentrate on creating one or both in an animal. The value of such models is dependent on the question to be addressed: for example, to study the consequence of a lesion or artificial pathology on the voiding phase; or to test a drug intended to reverse a voiding problem. For the latter it is important that the functional parameters in the animal model may be reversed to warrant testing of a drug. Various models have been constructed and these are discussed with respect to the addition of information to our current knowledge on DU below. Particular attention is given to ageing, age-related comorbidity, obstruction models, and specific neurogenic models for DU.

Ageing Models

To study "healthy ageing," animal models use the concept of a "healthspan" as an age range when an animal is generally healthy.[21] Human lower urinary tract dysfunction, prevalent at an age >65 years should be reflected in laboratory animals. Biomarkers associated with an ageing phenotype appear in mice and rats >18–24 months and guinea-pigs when >30 months.[22–24] In vivo, bladder contractile function may not diminish with age[25] but compliance and/or micturition frequency increase or decrease.[25–27] In vitro, contractility is either diminished or increased with age in both rats and mice.[26,28–30] Muscle loss may,[28] but not always increase with age: for example intravesical pressure at micturition actually increased with age in rats.[30] Moreover, motor nerve density is preserved in rabbits.[31] Afferent nerve density declines in ageing animals[32]; however, the age-related increase of urothelial transmitter release in the human bladder[33] has not been reproduced in animal preparations.

Overall, there are conflicting data on bladder function and morphology in ageing animals. It is crucial to characterize individual ageing animal models, using comparable criteria, to determine if their phenotype mirrors that of the ageing human and there is clearly still work to be done in seeking the ideal model which stands up as an adequate specific model for this purpose.

Diabetic Bladder Dysfunction (DBD) Models

Recognition of high rates of lower urinary tract symptoms (LUTS) in both type 1 and type 2 diabetic patients led to development of the term diabetic bladder dysfunction (DBD) as an umbrella description for a group of clinical symptoms.[34] DBD includes storage and voiding problems, as well as other less well-defined clinical phenotypes, such as decreased sensation and increased capacity. Portions of this spectrum of changes have been reported in other pathologies that result in LUTS such as bladder outlet obstruction, neurogenic bladder, and geriatric voiding dysfunction.[35,36] Although no single study has yet reported the cumulative effects on patients with type 1 or type 2 diabetes, it has been estimated from multiple studies that DBD is among the most common and costly complications of diabetes mellitus, affecting 87% of patients.[34]

In type 1 diabetes models, DBD seems to follow a characteristic progression, resulting in different phenotypes of lower urinary tract dysfunction in early and late phases. Early stage diabetes (<9 weeks in rodents) causes detrusor overactivity in both in vivo (cystometry) and in vitro (organ-bath) studies. In the later stage (>12 weeks in rodents), the detrusor loses its ability to expel urine or respond to in vitro stimuli such as electrical field stimulations. Therefore, it has been hypothesized that the result of end-stage DBD is an atonic or underactive detrusor[37] that is the result of long-term hyperglycaemia-related oxidative stress and polyuria.[38,39] There is a growing body of evidence to indicate that oxidative stress and inflammation are independently associated with obesity and diabetes. Furthermore, oxidative stress appears to contribute to complications of these disorders that include detrusor overactivity and geriatric bladder dysfunction,[40–42] it is plausible that the natural history of DBD could be replicated in other chronic conditions affecting the bladder such as obesity and ageing.

Obstruction and Bladder Overdistension Models

Bladder outlet obstruction (BOO) is a common precursor of LUTS in the ageing male population, leading to filling and/or voiding phase complaints.[43] However, whether a patient develops a higher post-void residual or eventual urinary retention is not only dependent on the grade of BOO. Numerous in vitro and in vivo animal studies have reported the bladder's response to acute or chronic BOO [44–48]. Several in vitro studies have shown a consistent relationship between increased bladder mass and altered contractile responses in muscle strips in prolonged BOO in rat, rabbit and cat preparations.[49–52] Some studies have even compared findings in animals to the human situation, mainly focusing on structural rather than functional changes.[53,54]

Current models mostly induce mechanical obstruction by placing a clip, ring, or suture around the urethra to induce partial BOO. While acute effects are seen in these models, the functional effects in partial BOO (pBOO) for longer times (>6 weeks in rat and rabbit, and >3 months in cats) seem to mimic the effects in human BOO relatively well. In these experimental conditions the bladder mass increases in proportion to the increase of bladder volume and the inability to empty completely. With experimentally-induced BOO in cats, deterioration of bladder function proceeded more slowly than in rats and rabbits and the functional and morphological state of a compensated bladder remain relatively stable[52]; this is also often seen in humans with BOO but occurs at a much slower rate. Thus pBOO models in rodents, rabbits, and cats can mimic some of the aspects of loss of contraction seen in DU. In these models reversibility of function after removal of the obstruction is often not seen. This is not a problem if one is interested in the developmental pathology of DU, but is if the model is to be used for drug-effect studies that might reverse obstruction.

Ischaemia/Oxidative Stress Models

The two main animal models to investigate in vitro oxidative damage are: *direct* bladder damage by hydrogen peroxide; or *indirect* induction via ischaemia followed by reperfusion.[55] Atherosclerosis-induced chronic bladder ischaemia significantly reduces detrusor contractility of rabbit[56] and rat bladders.[57] A general problem in these models is that the severity of effects is difficult to titrate and establish, leading to large variability of results. In vitro induction of oxidative stress, whether or not caused by artificial obstruction, led to a significant decrease in contractility.[55,58] Overall, in vitro as well as in vivo animal studies clearly show a correlation between oxidative stress and impaired contractility. One of the important remaining questions is to what extent reduction of oxidative stress can be utilized as a potential therapeutic target in humans.[59,60]

Neurogenic Animal Models

Besides age-related comorbidities, incomplete emptying is also common in patients with bladder dysfunction caused by specific neurological disease, including multiple sclerosis (0–40%),[61] Parkinson's disease (53%),[62] and multiple system atrophy (52–67%).[63] Several animal models have been designed to mimic specific neurogenic situations and relate these to altered contractility.[3] DU can span a spectrum from slightly decreased ability to generate intravesical pressure (that may in turn be compensated for by increasing outlet-opening capability) to a bladder that cannot generate any pressure for emptying upon neural activation. A canine model of lower motor neuron injury has been developed, resulting in an atonic bladder.[64] This spinal root transection model showed activation of different nerve tracts to the bladder after its reinnervation by transfer of the genitofemoral nerve,[65] indicating that there is plasticity in the end organ following bladder reinnervation.

Although the neurogenic models mimic specific situations, experimental results may not be applied to a wider group of DU patients, however, some reinnervation paradigms have already

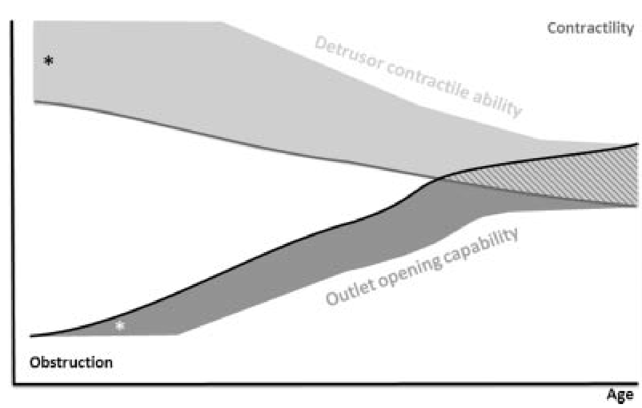

Fig. 1. Schematic hypothetical relationship between obstruction and detrusor contractility as a function of age. The diagram shows an increase of obstruction and subsequent decrease of detrusor contractility. Whether or not a patient develops detrusor underactivity over time is dependent on the capacity to compensate by increasing detrusor contractility (detrusor contractile ability or "contractile reserve") or alter bladder outflow relaxation (outlet opening capability). *Represents the rest compensatory capacity.

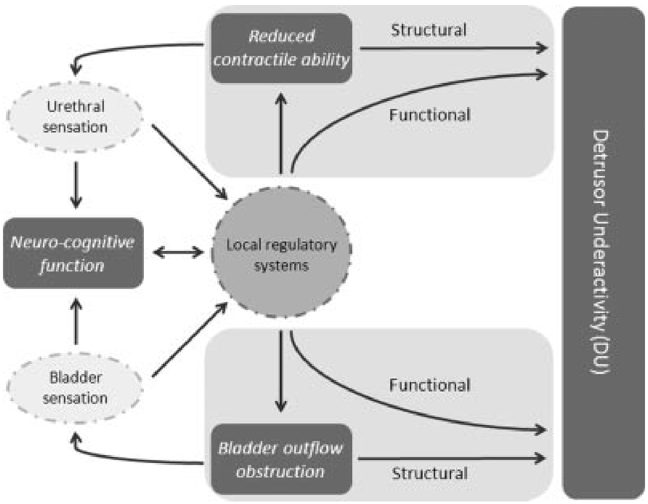

Fig. 2. Complexity of the interplay between factors involved in bladder emptying and detrusor underactivity. Structural and/or functional changes may result from reduced ability of the bladder to contract or bladder outflow obstruction (BOO). Changes to sensory pathways and to neuro-cognitive function could affect either of these two major causative pathways.

been tested in experimental human studies,[66] thus accentuating their importance and high translational value.

WHAT DATA DO WE NEED AND WHAT RESEARCH QUESTIONS SHOULD BE ADDRESSED IN THE FUTURE?

1. Development of study tools based on a system's pathophysiological approach

   Given that effective voiding is maintained via a complex balance between the compensatory capacity (or contractile reserve) of the bladder and the outlet opening capability of the bladder neck and urethra (Fig. 1), improvement of one or both compensatory and correctable mechanisms could potentially be used as a therapeutic target. More insight into the interplay of different mechanisms (Fig. 2) such as bladder and urethral sensation, urethral/bladder neck relaxation and detrusor contraction, all under neuro-cognitive control might give additional clues to explain ineffective bladder emptying.
   - Which clinical observations determine best detrusor compensatory capacity or infravesical relaxation capacity and might define patients at risk for DU?
   - How might the contributions of each factor be isolated and measured?
   - What is the role of bladder/urethral sensation and of neurocognitive regulation in DU?
2. Characterization of morphological and functional properties of isolated bladder wall samples

   Research to evaluate structural bladder and urethral changes in humans with DU should lead to better understanding of its aetiology.

   In vitro data from isolated human detrusor material should yield invaluable information about cell and tissue pathways that regulate detrusor contractility and urethral relaxation allowing exploration of the relationship between contractility and the clinical observation of impaired contractile function This may be related to confounding factors in in vitro preparations that influence contractile output, but unrelated to muscle contractility per se, including: altered connective tissue content; detrusor denervation and enhanced neurotransmitter secretions from other tissues, such as the mucosa.[3,16,67] Moreover, factors other than changes to bladder wall tension (in principle true detrusor contractility) affect the ability of the bladder to raise intravesical pressure, including: outflow tract resistance; initial bladder volume; and bladder geometry.[68]
   - What structural bladder and urethral changes in humans are associated with the development of DU?
   - What is the relationship between morphological and functional properties of isolated bladder wall samples and resultant LUT function from bladders yielding those biopsy samples?
3. Correlation of in vitro and in vivo data

   Likewise, such exploration of in vitro and in vivo human material should allow additional insight into the translational nature of existing animal models.
   - What is the relationship between in vitro data and in vivo function in animal models of DU?
4. Development of more comprehensive models

   Currently, most animal models represent a specific disease state to explain DU, for example diabetes or BOO, therefore for every model a translational step to a comparable human conditions should be made.
   - Which comprehensive animal models can we develop based on clinical observations and pathophysiological considerations.
5. Longitudinal data; needed for defining risk groups and development of screening tools

   In human DU multiple factors are most likely simultaneously involved. This multifactorial nature makes it challenging to define whether a drug, tested in experimental animals, will have a substantial effect in clinical urological practice. Therefore, determination of urodynamic or history-based indicators for DU is necessary for detection, diagnosis and follow-up after therapy. In addition, there is a need for longitudinal studies in LUTS patients to define the factors, which place patients at risk for developing DU.
   - What are the urodynamic or history-based indicators, associated with DU, which are required for detection, diagnosis and follow-up after therapy?
   - Are there specific pathological markers, which could allow definition of at risk groups?
   - Is there potential for a non-invasive screening tool to predict at risk patients?

Focus of future DU research	Animal studies	Human studies
1 Development of study tools based on a system's pathophysiological approach	✓	✓
2 Characterization of morphological and functional properties of isolated bladder wall samples	✓	✓
3 Correlation of in vitro and in vivo data		✓
4 Development of more comprehensive models	✓	
5 Longitudinal data; needed for defining risk groups and development of screening tools		✓

ACKNOWLEDGMENT

Portions of the results on "neurogenic animal models" were supported by Award Number R01NS070267 from the National Institute of Neurological Disorders and Stroke. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.

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