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Could A Better Understanding of The Underlying Pathophysiologies Lead to More Informed Treatment Choices in Patients with Lower Urinary Tract Dysfunction Due to An Acontractile or Underactive Detrusor? ICI-RS 2023

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Abstract

Introduction

The underlying pathophysiology behind a diagnosis of acontractile or underactive detrusor at invasive urodynamics is very heterogeneous. Lack of etiological classification currently limits the possibility of stratifying therapy.

Methods

This subject was discussed at a think-tank on the subject at the International Consultation on Incontinence- Research Society (ICI-RS) held in Bristol, June 2023. This manuscript is a result of those deliberations and the subsequent discussions of the think-tank.

Results

There are challenges in defining abnormalities of detrusor contraction with resultant implications for available evidence. Pathology at any level of the neuromuscular pathway can impair or prevent a detrusor voiding contraction. Attempts have been made to identify clinical markers that might predict an underactive detrusor but strong supporting evidence is lacking. Hence, a holistic approach to phenotyping requires specialized neuro-imaging as well as physiological investigations. Several general measures can help individuals with an abnormal detrusor contraction. The search for a molecule to enhance the detrusor voiding contraction remains elusive but there are promising new candidates. Neuromodulation can help select individuals but data is not well stratified by underlying etiology. Manipulation of central neurotransmitters might offer an alternate therapeutic option.

Conclusions

A better understanding of the underlying pathophysiologies behind an abnormality of the detrusor voiding contraction is needed for improving management. Towards this goal, the think-tank proposes a classification of the underactive detrusor that might help in selecting and reporting more well-defined patient cohorts.

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An abnormality of detrusor contraction is commonly encountered on invasive urodynamics evaluation in patients with refractory voiding symptoms.[1] While lower urinary tract symptoms can result, the proportion of asymptomatic individuals in the general population with such an abnormality is unknown.[2] Contraction abnormalities can range from varying degrees of underactivity to a complete failure of contraction (acontractile detrusor).

A diagnostic label of acontractile or underactive detrusor does not clarify the underlying pathophysiology. It is uncertain whether acontractility should simply be regarded as one end of a spectrum of underactivity as there is no clear evidence that underactivity progresses to acontractility.[3] Pathophysiological diagnosis is challenged by limitations in our technology, understanding, and terminology. This in turn limits our ability to stratify therapy. Unsurprisingly, guidelines fail to give specific recommendations.[4,5]

This manuscript is the result of discussions of a think-tank at the International Consultation on Incontinence- Research Society (ICI-RS) held in Bristol, June 2023. The discussions assume the absence of any concomitant obstruction (functional or structural).

Definitions and Epidemiology

Currently, the term 'acontractile detrusor' is recommended when the detrusor fails to contract during pressure-flow testing[2] and there is a known underlying cause or reason (clinically consistent), and 'situational inability to void' when this is unexplained.[6] The term 'contractility' should only be used in the context of specific steps taken to elicit the limits of detrusor contraction power.[7] The joint International Continence Society and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction Society (ICS-SUFU) Standard recommends use of the term 'detrusor underactive voiding contraction' when the detrusor voiding contraction is observed to be below a specified limit based on pressure-flow analysis.[7] The term is also applied when the detrusor contraction is of insufficient duration.

Assessment of detrusor contractility needs standardization of a tool for measurement of contraction power along with a threshold for defining what should be regarded as abnormal. The ICS-SUFU standard recommends use of the (new) term Detrusor Contraction Index (ICS-DCI) based on a projected isovolumetric pressure calculation given by the formula $p_{det.Qmax} + 5 \times Q_{max}$. The standard recommends the use of very weak, weak, normal, and strong detrusor voiding contraction for ICS-DCI values of <50, 50-100, 100-150, and >150. In women, this projected isovolumetric pressure tends to overestimate contraction power leading to a more realistic formula defined as $p_{det.Qmax} + Q_{max}$ (captured from pressure-flow study, not 'free' flow) also known as PIP1.[7] The standard accepts the principles of both DCI as well as PIP1 in women. DCI >100 clearly indicates a normal detrusor and values of less than 30 on PIP can generally be regarded as underactive. However, there is lack of good data for defining cutoffs in women.[7]

Detrusor voiding function is not well standardized for the neurogenic population. It is uncertain how this might influence the interpretation of contractility in the elderly population with possible concomitant geriatric neuro-urological conditions.

The prevalence of detrusor contraction abnormalities in the general population is unknown and might be difficult to study given the practical difficulty of performing population-based invasive urodynamics studies. Clinical underactive bladder, which might identify a group of individuals at higher risk of harboring an underactive detrusor is often noted in the general population.[8]

Confounders

Scientific literature has several confounders that limit the applicability of clinical data with regard to detrusor contractility. Apparent acontractility can result from failure to elicit a contraction during urodynamics testing in someone who might otherwise be expected to void, termed 'situational inability to void'.[7] This can become a judgement call by the clinician. Published literature is also influenced by differing policies with regard to performing urodynamics. For instance, a 65y male with prostate size 40g and 400ml residual urine might undergo surgery without resorting to urodynamics, or have urodynamics after indwelling catheter, after instituting intermittent catheterization, or directly without draining the bladder. Each of these policies is likely to yield different data. This in turn, would impact the available evidence.

Women with refractory voiding symptoms should ideally undergo advanced testing rather than a regular pressure flow test. Unfortunately, this is often not the case. For example, a young woman with apparent acontractility may or may not undergo video-urodynamics or urethral pressure profilometry which might enable a more specific diagnosis such as 'high tone non-relaxing sphincter' *(Caution: lack of ICS terminology)*.[9]

Neuromuscular pathways involved in detrusor contraction

The bladder stores and voids urine from the kidneys under control of sensory and autonomic nervous systems. The autonomic sympathetic and parasympathetic neurons that innervate the bladder are located in the inferior hypogastric plexus (also called the pelvic ganglia), the only structure in the body where neurons of both branches of the autonomic nervous system are found together. Pre-ganglionic sympathetic axons from the lumbar spinal cord synapse with sympathetic neurons in the inferior hypogastric plexus, while parasympathetic axons projecting from the sacral spinal cord synapse with parasympathetic neurons. During filling, sensory nerves from the bladder signal to the central nervous system and brain to maintain activation of sympathetic system. These nerves release neurotransmitter noradrenaline to activate beta-adrenergic receptors on the bladder smooth muscle, maintaining an active relaxation of the detrusor, ensuring compliance and low-pressure filling. When sensory nerves sense fullness, urination is initiated by higher centers in the brain. The sympathetic nervous system is switched off and the parasympathetic autonomic nervous system switched on. Parasympathetic axons release neurotransmitters, such as acetylcholine and ATP, to activate muscarinic and purinergic receptors on the smooth muscle and initiate detrusor contraction. This occurs in coordination with relaxation of the striated skeletal muscle in the urethra and pelvic floor mediated by somatic pudendal nerve efferents as well as relaxation of the smooth muscle at the bladder neck via autonomic pathways, resulting in complete urinary voiding.[10,11]

Pathogenesis of abnormal contractility

Pathology at any level of the neuromuscular pathway can impair or prevent a detrusor voiding contraction.

Abnormalities of the detrusor muscle can impair contraction. These could involve different components of the contraction mechanism including the contractile proteins and filaments, cytoskeleton, actin-myosin interaction, cellular metabolism, and mechanical properties of the detrusor muscle.[10] These abnormalities are associated with distinctive ultrastructural changes.[12,13]

Damage to the efferent neural mechanism at any point can lead to aberrations in detrusor contraction. This might be at the level of neuromuscular end plate, peripheral nerves, spinal pathways including interneurons, or the pontine micturition center. Many of these may also impact the outlet and play a role in determining the resultant pathology but are outside the scope of this discussion. An abnormality in the afferent signals from the bladder can affect initiation of a voiding detrusor contraction by the cortical limbic system. These afferents travel from receptors in the bladder wall via peripheral afferent nerves, through the spinal cord and periaqueductal grey matter to the thalamus.[14]

Deficiencies of neurotransmission in the suprapontine autonomic nervous system are possibly responsible for some of the detrusor contraction abnormalities noted in degenerative brain conditions and might underpin the concomitant finding of detrusor overactivity during filling and detrusor underactivity during voiding in some individuals. Dopamine deficiency has been noted in patients with Parkinson's disease, multiple system atrophy, and Lewy body dementia, as well as genetic disorders such as restless legs syndrome, even among pediatric populations. Aging can potentially impact voiding at all levels. There is a decrease in detrusor contraction strength in the elderly but the underlying mechanisms are not well studied. There is general decline in central neurotransmission including reductions in dopamine, serotonin, and catecholamines, all of which can result in autonomic dysfunction as well as changes at the level of the detrusor muscle.[14,15]

An association has been noted between mental health problems and lower urinary tract symptoms, possibly bi-directional, with mental health and refractory lower urinary tract symptoms affecting each other. The association might involve corticotropin releasing factor.[16] Adverse childhood experiences and stress can result in a cascade of pro-inflammatory cytokines and chemokines at the central as well as peripheral level resulting in altered lower urinary tract function. Voiding abnormalities have been shown to occur including underactivity.[16–18] Mental health problems can impact several areas of the brain that are associated with voiding function including the hypothalamus, amygdala, insula with projections to the pontine micturition center. These key areas of the limbic system involved with emotion send neuronal inputs to the micturition center and might explain this association.[14,19] Psychological problems are also associated with an overactive pelvic floor. Marked overactivity of the pelvic floor may be associated with failure or partial inhibition of the voiding reflex.

Genetic conditions associated with detrusor contractility disorders are not well studied. However, animal models of the urofacial syndrome in mice suggest that gender might play a role in determining whether underactivity results.[20]

Diagnosing and phenotyping patients with abnormal detrusor contractility

Attempts have been made to identify clinical markers that might predict an underactive detrusor. The Japanese Continence Society defined clinical diagnostic criteria comprising of a characteristic symptom complex (voiding symptoms of slow stream, hesitancy and straining to void, and often reduced sensation of filling) along with maximum flow rate <12ml/s, residual urine >100ml, and bladder voiding efficiency <90% along with intravesical prostate protrusion <10mm and/or prostate volume <30ml in men or absence of significant pelvic organ prolapse (cystocele up to stage II).[8] However, strong supporting evidence for such criteria is lacking.

The initiation, magnitude and duration of the detrusor contraction during the voiding phase may be compromised due to dysfunction at supra-pontine, pontine, spinal, peripheral nerves, neuromuscular junction, or detrusor muscle levels **(Table 1)**. Neurophysiological studies and imaging can help identify the etiology. However, the pathology might lie at more than one level and might not always be clear.

Supra-pontine and pontine Level: Pre-requites for normal detrusor voiding contraction include normal bladder sensation, the individual's decision-making (based on environmental, emotional and social factors), an ability to switch from filling phase to voiding phase, and co-ordination of detrusor-sphincter function. Activation of brain centers responsible for these four functions can be reliably assessed by functional magnetic resonance imaging during voiding.[21] The neuroanatomy of these brain centres and connectivity may also be assessed using diffusion tensor imaging.[22]

Spinal and peripheral nerves level: Spinal lesion or peripheral neuropathy may result in primary or secondary detrusor underactivity. The spinal cord and peripheral nerves can be visualized with traditional magnetic resonance imaging or ultrasound techniques. However, these methods are qualitative unless a clear transection has occurred. Diffusion tension imaging can provide visualization of the peripheral nerves whilst also generating quantitative parameters that can be used to assess axonal integrity and nerve function.[23] Numerous studies have demonstrated the potential of such imaging in assessing the lumbar-sacral plexus in individuals with and without neuropathy.[24,25]

Detrusor muscle: Anatomical "quality" of the detrusor muscle may be assessed by quantifying the degree of fibrosis using ultrasound elastography.[26] Pressure-flow analysis may also be used to understand the cause and (any) progress of underactivity in the non-neurogenic setting. An overactive hypertrophied external urinary sphincter may have an inhibitory effect on the detrusor muscle, and this may be assessed using urethral pressure profilometry, ultrasound sphincter volume, and sphincter electromyography.[27]

Evidently, a holistic approach to phenotyping is required including imaging as well as physiological investigations, to identify the exact cause of abnormal detrusor contractility.

Framework for an Etiopathogenesis-Based Approach to Treatment

Management of the underactive or acontractile detrusor can take several approaches. General measures such as double voiding and avoiding overhydration or diuresis-inducing substances in the diet can help by preventing the bladder from becoming overfilled, regardless of the underlying pathology. Reduction of any outlet obstruction by medication or surgery aimed at the bladder neck/prostate can help. Men with voiding symptoms and an underactive detrusor can benefit from prostate surgery especially if they have concomitant obstruction. There is little data on alpha blockers or bladder neck incision surgery in women with an underactive detrusor. Bladder emptying by intermittent catheterization is the standard

recommendation for poor bladder emptying, while indwelling catheters (urethral or suprapubic) are a last resort most often used in the geriatric or quadriplegic population.

Use of suprapubic pressure or Valsalva voiding to augment or substitute bladder contraction are at best modestly effective and generally discouraged. Inadvertent opposition by the pelvic floor can result in unsafe pressures and patients can develop herniae.[28] Another reported method of augmenting bladder power entails surgically wrapping the bladder with skeletal muscle.[28] More recently, intra-urethral powered devices have been designed to be inserted into the urethra but have a high discontinuation rate.[5]

Other options are discussed below as part of an etiopathogenesis-based approach.

Myogenic

The quest for medication to improve detrusor power remains elusive. Parasympathomimetics such as bethanechol and cholinesterase inhibitors such as distigmine fail to improve coordinated voiding and guidelines specifically recommend against them.[28] Other molecules studied include prostanoids (such as Prostaglandin E2), bladder-specific parasympathetic agents (such as acotiamide), muscarinic receptor manipulation (ASP8302), neurokinins (DTI 100), and TRP channel agonists.[29] A different approach has been the intra-detrusor injection of stem cells or use of gene therapy.[29,30] In an experimental model, enhanced detrusor contractility has been noted following injection of human mesenchymal stem cells with enhanced hepatocyte growth factor expression into the rat detrusor muscle.[31] Autologous muscle-derived stem cells have been harvested from the quadriceps, processed to isolate autologous muscle derived stem cells, and injected into the detrusor in a promising clinical study.[29]CHANCELLOR More recently, partial blockage of the enzyme purine nucleoside phosphorylase by 8-amino guanine has shown promise in age-associated detrusor muscle weakness in rat models.[32] Currently, none of these agents are recommended in clinical practice.

It is possible that myogenic causes include a variety of different pathologies and that some of the aforementioned therapies might work in an as yet undefined sub-set of patients.

Peripheral Nerve

A pilot study that examined the effect of injection of autologous muscle derived cells included patients with iatrogenic peripheral nerve injury related loss of contractility but failed to provide results stratified by underlying etiology.[33] Other studies suffer from a similar limitation for instance, including diabetic patients without clarifying whether this diagnosis was causally linked with the diagnosis.[34]

The ICS Best Practices Statement suggests that patients with a lower motor neuron injury might be less likely to benefit from sacral neuromodulation (SNM).[35] A recent review of patients with neurogenic lower urinary tract dysfunction showed successful test phase results in 52% of patients with 'non-obstructive' voiding difficulty. Cohorts studied included patients who might be expected to have had a peripheral nerve lesion. Results were however not stratified by the underlying disease making it difficult to ascertain or predict outcome in individual patient groups.[36]

Spinal Neurogenic

Patients with spinal injury or disease often show concomitant abnormalities of the outlet that can impact management. A study of SNM included 29 patients with spina bifida. 26% 'improved' their flow (6.8±4.71 ml/s to 10.4±4.45 ml/s; n.s.).[37] Of note, none of them recovered a normal detrusor contraction. A recent review concluded that patients with voiding difficulty might benefit. Cohorts studied included patients

with multiple sclerosis, spina bifida, and incomplete spinal cord injury. Results were not stratified by underlying disease and it was not always possible to ascertain whether the underlying condition affected the upper motor neuron, lower motor neuron or both.[36] The mechanism of any improvement remains uncertain.

Use of SNM is off-label in patients with spina bifida or spinal cord injury. The ICS Best Practices Statement gives a Grade C recommendation for the use of SNM for symptom control in patients with low-risk neurogenic lower urinary tract dysfunction that would exclude such patients.[35] The AUA guidelines regard spinal cord injury as a contraindication.[38]

Suprapontine

While a decline in central neurotransmission has been shown to be associated with autonomic dysfunction in the elderly, there is little evidence with regard to using this hypothesis for augmenting detrusor contractility. Use of dopamine agonist in a monkey model of Parkinsonism did not appear to increase the strength of the detrusor contraction.[39] However, urodynamics in patients before and 1 hour after a 100mg dose of levodopa showed an increase in detrusor contraction strength with both symptomatic and urodynamic improvement.[40] Similar but weaker effects have been seen with bromocriptine.[41] In clinical practice, however, dopaminergic agents do not seem to reduce the postvoid residual urine. Some gender-based differences were noted in the strength of detrusor contraction with no impact of medication in men and a variable impact in women depending on the severity of their neurological symptoms.[42] Apomorphine does not result in any improvement in detrusor contractility.[43] Use of rasagiline, a MAO inhibitor resulted in 53% reduction in residual urine but no impact on voiding IPSS-subscores.[44] Safinamide, a MAO-b inhibitor did not result in change in non-invasive uroflow rate.[45]

Therapies directed at mental health disorders such as cognitive behaviour therapy, breathing techniques and skeletal muscle relaxation are all also part of the management of patients with an overactive pelvic floor which might outlet.[46] A history of mental health disorder increased SNM success OR 3.92 in women.[47] However, the site of action of such therapies is uncertain.

Terminology and Proposed Classification

Current ICS terminology (*vide supra*) does not take into account the underlying etiology of detrusor muscle weakness. Lack of such classification has drawbacks. Researchers fail to study and present data stratified by the underlying etiology. This might result in failing to find a therapeutic benefit where one exists, simply because the study cohort included an incorrect set of patients. For instance, it might not be appropriate to include acontractility related to radical pelvic surgery for a study of central neurotransmitter manipulation. It also results in largely unusable data because the underlying spectrum of conditions is so diverse. A major argument against such classification would be the large pool of idiopathic patients. One would expect this group to become smaller with more research into the field.

This working group of ICI-RS would like to suggest a classification for DU that follows the ICS classification of DO. We hope ICS will consider our proposals on the terminology as an aid to communications on this lower urinary tract dysfunction (Table 2).

Avenues for research

The working group identified several important areas for future research. **Table 2** lists some important domains along with suggestions for study design.

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