

W3: Lower Urinary Tract Biomechanics: Physiological & Clinical Implications

Workshop Chair: Margot Damaser, United States

26 August 2013 14:00 - 17:00

Start	End	Topic	Speakers
14:00	14:20	Overview of lower urinary tract biomechanics	• Margot Damaser
14:20	14:30	Questions	All
14:30	14:50	Urethral biomechanics - Implications for normal physiology and pathophysiology	• Matthew Fraser
14:50	15:00	Questions	All
15:00	15:20	Interaction between bladder mechanics and physiological response	• Longkun Li
15:20	15:30	Questions	All
15:30	16:00	Break	None
16:00	16:20	Implications of biomechanics on pathophysiology	• Maryrose Sullivan
16:20	16:25	Questions	All
16:25	16:45	Clinical implications of lower urinary tract biomechanics	• Christopher Chermansky
16:45	16:50	Questions	All
16:50	17:00	Discussion	All

Aims of course/workshop

This workshop will provide an overview of lower urinary tract biomechanics and its relationship to Urodynamics, physiology, and pathophysiology. The two primary functions of the lower urinary tract, filling and voiding can be described in biomechanical terms. This workshop will review developing theories regarding the relationship between bladder mechanics and the physiological responses at the whole organ, cellular, and molecular levels. We will also relate biomechanics to pathophysiology and clinical treatments of lower urinary tract dysfunction. This workshop should provide the background for researchers and clinicians to test their own theories regarding lower urinary tract biomechanics and its impact on lower urinary tract physiology.

Overview of Lower Urinary Tract Biomechanics and Introduction of Speakers

Margot S. Damaser, Ph.D., Chair

The chair will begin with an introductory talk that provides an overview of the field with an emphasis on biomechanics of the bladder and urethra during filling in the storage phase. Lower urinary tract function consists of two phases: storage and emptying. During the storage phase the bladder needs to store urine at low pressure until a convenient time to void. This means the urethra needs to remain closed and maintain pressure above that of the bladder to prevent leakage. To maintain full continence, the urethra must maintain sufficient closure against increases in bladder pressure such as during coughing, laughing or other activities. To maintain low pressure, the bladder must be a compliant vesical. In biomechanical terms, this means it can stretch easily without exertion of much force to increase volume. Compliance of a smooth muscle/connective tissue organ, such as the bladder, can be affected by activation or inhibition of motor and sensory innervation, muscle contraction and relaxation, fibrosis, increase in thickness as in hypertrophy, change in shape of the bladder, and almost any other change to the organ. So, for example, bladder pain and irritability can trigger reflexes that cause bladder instability and nonvoiding contractions, decreasing compliance and reducing the ability of the bladder to store sufficient urine until a convenient time to void. Therefore, the primary function of the bladder during the storage phase can be described in biomechanical terms and any treatment aimed at restoring normal storage function and reducing incontinence can be characterized quantitatively using principals of biomechanics in addition to the usual molecular, cellular, pharmacological, and behavioral characterization of treatments.

During voiding, the urethra must relax and reduce the closure pressure it has maintained during the storage phase. The bladder must contract at sufficient pressure to overcome any residual resistance in the urethra and for a sufficient length of time so as to fully empty. Failure of any of these aspects of normal voiding can lead to voiding dysfunction. Similar to the storage function of the bladder, voiding function can be affected by activation or inhibition of motor and sensory innervation, muscle contraction and relaxation, fibrosis, increase in thickness as in partial outlet obstruction, hypermobility of the urethra, denervation and atrophy of muscles, changes in muscle and nerve function with aging, and almost any other change to the organ. Also, similar to the storage phase, voiding, voiding dysfunction, and treatments for voiding dysfunction can be characterized quantitatively using principles of biomechanics.

Dr. Fraser will provide a review of biomechanics of the bladder and urethra with a particular emphasis on how the biomechanics of the urethra during voiding affects normal bladder physiology during voiding. Dr. Li's presentation will take the program to a molecular level as he presents the results of his research and reviews the research of others on the molecular mechanisms of stretch in bladder contraction. He will review the classic neuroregulation mechanisms and report on recent molecular signaling findings which modulate stretch-induced bladder contractions in which the interstitial cells of Cajal (ICC)-like cells take a prominent role. Dr. Sullivan will review the data relating lower urinary tract biomechanics to pathophysiologies of the lower urinary tract such as overactive bladder and interstitial cystitis with an emphasis on molecular outcomes. She will discuss how changes in lower urinary tract biomechanics can impact pathophysiological outcomes as well as how changes to molecular and cellular biology in pathophysiological states can in turn impact lower urinary tract biomechanics. Her talk will set the stage for a discussion on pathophysiological based treatments aimed at restoring lower urinary tract biomechanics to normal. Dr. Chermansky will provide clinical insights into the effect of therapeutic treatments on pathophysiology and lower urinary tract biomechanics. His talk will, as a result, relate the previously presented research to clinical outcomes. In addition, he will add insights on the molecular, cellular, and other mechanisms by which pharmacological therapeutics can improve lower urinary tract biomechanics.

Urethral biomechanics: Implications for normal physiology and pathophysiology

Matthew Fraser, Ph.D.

- Dr. Fraser will review biomechanics of the bladder and urethra during storage and voiding phases, with a particular emphasis on how the biomechanics of the urethra during voiding affects normal bladder physiology

The bladder and urethra are terms that best describe the lower urinary tract during filling or at rest, implying that they are anatomically distinct regions. In fact, the two “compartments” share continuous longitudinal muscle layers that extend into both, implying a single unit. This single entity has been referred to as the vesicourethral muscularis, and forms a single functional unit during the void. It is true that during filling, the functional units of the urethra and the bladder exist as separate compartments, with the urethra contracted circumferentially. Dogma tells us that filling of the bladder from the ureters is a passive process, driven by the peristalsis of the ureters. Recently, however, time-lapse photography of the bladder during filling has shown that the bladder base undergoes peristaltic-like waves that propel fluid into the dome. Thus during filling, the bladder functions as a two compartment system (albeit with a shared lumen). As mentioned above, at the time of a micturition, the vesicourethral muscularis forms a single functional unit, with contraction of the longitudinal smooth muscle system together with relaxation of the urethral circumferential smooth muscle layer resulting in a funneling and longitudinal shortening of the bladder base-urethral region, while the dome contracts in an isotropic fashion, resulting in efficient emptying of bladder contents.

Obviously, the coordinated execution of the symphonies of muscle layer contractions and relaxations that must occur for proper filling and voiding depends greatly on the biomechanical properties of the layers. Disease states can affect not only the passive biomechanical properties of the tissues (e.g. extracellular matrix), but also the active biomechanical properties (e.g. intrinsic myogenic tone/activity and neural influences). Passive and active influences may be disparate, for example the bladders of suprasacral spinal cord injured may be passively compliant, but actively non-compliant. Additionally, single direction changes in passive

biomechanical properties, such as fibrosis, would result in both an inability to relax and to contract effectively.

We will review the anatomy and physiology of the lower urinary tract and provide examples of how altered biomechanical properties due to specific disease states can contribute to dysfunction.

The molecular mechanisms of stretch in bladder contraction

Longkun Li, M.D.

The main function of the bladder is the storage and discharge of urine. Sympathetic and parasympathetic innervation of the detrusor play a leading role during the filling phase as well as during stretch-induced bladder contraction. Recently, via molecular biology techniques, research has focused on the molecular mechanisms of stretch-induced bladder contraction. The goal of this talk is to review the classic neuroregulation mechanisms and report on recent molecular signaling findings which modulate stretch-induced bladder contractions.

The first step in the molecular mechanism of stretch-induced bladder contraction is the release of non-neuronal ACh, located in the epithelial cells of the bladder by stretch stimulation during the storage period of bladder function. Thereby ACh activates the M2 and M3 cholinergic receptors on epithelial cells, converting the mechanical signals of stretch into chemical signals. Subsequently, adrenergic receptors such as P2X₆ in the Interstitial Cells of Cajal (ICC)-like cells under the lamina propria of the mucosa are activated by ATP. The contraction is then transmitted along the bladder ICC-like cells by Cx43 gap junctions, and re-integrated into electrical or chemical signals passed to the bladder smooth muscle. In addition, ATP directly activates P2X₃ receptors and then acts on smooth muscle cells via TRPA1, TRPV4 and TRPM8 from the transient receptor potential (TRP) family of receptors. These receptors are known to participate in sensation of cold, heat and other stimulation, and can initiate afferent stimulation to the central nervous system micturition centers.

When the bladder receives an efferent signal from the central nervous system micturition centers, ACh is released for parasympathetic stimulation and the muscarinic receptors, M2 and M3, are activated. While the M2 receptors can suppress the adrenergic receptors, the M3 receptors are primarily responsible for contraction of the bladder. Resultant activation of calcium ion channels leads to enhancement of intracellular calcium, which integrates with troponin and myosin and triggers a stretch-induced contraction. Stretch-activated ion channels (SACs) contribute to the molecular mechanisms of stretch contraction, and below we describe the evidence for step by step process of activation of various types of ion channel.

1. Smooth muscle cells: Via the patch clamp technique, a variety of receptors and ion channels have been suggested to involve in the stretch-induced contraction:

(1) In 1993, Using guinea pig, Wellner et al first identified a class of SACs in bladder smooth muscle cells. The activation of SACs during the storage phase facilitates the inward flow of

calcium ions which increases intracellular calcium concentration and mediates detrusor smooth muscle contraction.

(2) In 1994, further study from Wellner's team revealed that the SACs and voltage-gated L-type calcium ion channels participate in stretch-induced bladder smooth muscle contractions. Moreover, voltage-gated calcium channels and potassium channel have a negative feedback mechanism on this process.

(3) Ensuing studies demonstrated that calcium ions play a role in the regulation of bladder smooth muscle contraction. In rabbits, stretching bladder smooth muscle leads to the accumulation of intracellular calcium via activation of RYR receptors which is not related to the InsP3R mechanism.

(4) TRPV1, one of the major subtypes of vanilloid receptors, plays an important role in bladder contraction. Activation of the TRPV1 receptor can initiate the stretch-induced smooth muscle contraction mechanism.

(5) During the filling phase, detrusor smooth muscle contraction is almost absent to ensure stabilization and minimization of the bladder lumen pressure. To reduce bladder contractility, TREK-1, a stretch-activated potassium channel is activated.

2. Epithelial cells: Detrusor myocytes and urinary tract epithelial cells are thought to be able to avoid infiltration of urine. Recent studies have indicated that several receptors in the epithelial cell membrane regulate neurotransmission during bladder stretch.

(1) The first non-adrenergic non-cholinergic (NANC) receptor found in cultured human bladder epithelial cells was the P2X3 receptor, indicating that the epithelial cells participate in bladder sensation and contraction. ATP release can be thought of as one of the initiators of bladder contractions.

(2) Stretch of bladder epithelial cells. ATP released by bladder epithelial cells can be inhibited by the NHE inhibitor amiloride. The experiment further confirmed that amiloride blocks the epithelial sodium channel (ENaC) involved in bladder stretch. It subsequently was found to be expressed in bladder epithelial cells include three subtypes α , β , γ . All three subtypes have been found to be involved in control of ATP release.

(3) Acid-sensing ion channels (ASICs), a kind of H^+ ion channel related to ENaC channels, including the isoforms ASIC1 and ASIC2, are expressed in bladder epithelial cell membrane. Similar to the function of ASIC channels in the gastrointestinal tract, they modulate stretch sensitivity in the urinary bladder.

(3) TRP is another important ion channel family found in the bladder epithelial cell membrane. Its isoforms include: ① TRPV1b, which is activated by hypertonic contraction and may regulate contraction due to bladder stretch. ② TRPA1 has been reported to mediate bladder smooth muscle contraction, and its over-expression may be a pathophysiological factor involved in development of OAB. ③ Using TRPV4 knockout mice, previous studies have indicated that the contractility of the bladder was substantially attenuated, suggesting a regulatory effect of TRPV4 on bladder contraction. Further study found that the function of TRPV4 was triggered by the influx of calcium and the release of ATP.

3. ICC-like cells: Our previous study suggested that the ICC-like cells in the bladder may have a spontaneous excitatory function. However, the exact mechanisms have not been well elucidated.

(1) ICC-like cells are spontaneously active during bladder filling. With immunofluorescence double staining and patch clamp techniques, we found the presence of spontaneous electrical activity of ion channels in rat and human bladder at the ICC-like cell surface.

(2) Using in vitro detrusor muscle strips, we demonstrated that the application of Glivec, a specific ICC-like cell blocker, can significantly reduce detrusor muscle contraction intensity and signal transduction of the ICC-like cells.

(3) Previously, we proved that L-type calcium channel blockers did not reduce bladder ICC cell-induced spontaneous calcium influx and frequency. However, an ensuing study discovered that the T-type calcium ion channels can significantly reduce these spontaneous calcium flickers and attenuate the frequency and amplitude of the bladder contraction. The evidence for bladder ICC-like cells in stretch-activated spontaneous excitatory activity and signal transfer function provides more evidence, but still need further study.

Implications of Biomechanics on Pathophysiology

Maryrose Sullivan, Ph.D.

Micturition is a complex physiological phenomenon that is ultimately determined by the properties of a mechanical system. Substantial mechanical deformation of the bladder occurs during repeated cycles of bladder filling and voiding. Throughout this process, bladder smooth muscle transforms chemical and hormone signals generated centrally or locally, as well as physical cues, into changes in length and force development. Thus a fundamental property of smooth muscle is its relationship between force and the derivative of length (velocity). This hyperbolic relationship is defined broadly by the Hill curve, in which the velocity of shortening depends on the load against which it shortens. At the organ level, the force-velocity relationship is described in terms of bladder pressure and circumferential shortening velocity or flow. This relationship can be characterized by 2 parameters (P_{max} , v_{max}) assuming the curvature of the hyperbola is constant. Various clinical methods of assessing bladder contractility were derived from this basis.

Alterations in contractile function that can be measured urodynamically are common in many bladder pathologies. In men with symptomatic obstructive voiding dysfunction, detrusor contractility characterized by maximum isovolumetric contraction pressure is increased as a compensatory response to chronic outlet obstruction. The magnitude and slope of the isovolumetric detrusor contraction are elevated in patients with detrusor instability regardless of the presence of obstruction. Moreover, patients with detrusor overactivity (idiopathic or associated with obstruction) have increased shortening velocity of contraction. An age related decrease in shortening velocity has been reported; however changes in isometric pressure with age have not been clearly shown. In contrast, post-prostatectomy incontinence is associated with bladder underactivity, detected by low isovolumetric bladder pressure.

A lumped parameter theoretical model and its mechanical analog were developed to explore the functional properties of the bladder and outlet during voiding. In addition to pressure losses due to intrinsic resistance in the bladder, proximal resistance, and sudden geometry changes in the bulbous urethra, the pressure losses distal to the flow controlling zone were included in the theoretical model. The model predicted that normal subjects with low opening pressure and low pressure-area slopes void at subcritical flows and abdominal straining can augment flow. In contrast, prostatic obstruction shifts the transition flow to the critical regime and prevents straining induced improvement in flow. In the mechanical analog, an increase in opening pressure increased the slope of the pressure-flow relationship which became steeper

with decreased prostate compliance, suggesting that a reduction in prostatic compliance exacerbates the severity of obstruction.

Based on our understanding of changes in bladder contractile function and flow through collapsible tubes, a simple screening test for diagnosing prostatic obstruction was developed. By compressing the penile urethra after initiation of flow, the entire lower urinary tract is filled with urine and exposed to isometric bladder pressure, thus creating an isobaric system from the bladder to the site of penile urethral compression. The relatively more compliant bulbo-penile urethra, upstream of the compression site, becomes distended commensurate with the strength of detrusor contractility and the duration of the penile compression. Upon release of compression, the pressurized bulbo-penile urethra upstream of the urethral compression site discharges a surge of flow before steady flow is established. The degree of this initial flow surge thus depends on the magnitude and the rate of increase in the isometric contraction pressure, as well as the capacitance and hysteresis of the urethral segment proximal to the compression site. The subsequent flow rate during the restoration phase will depend on the degree of obstruction at the flow controlling zone located upstream of the penile compression site.

Various cell types in the bladder respond to changes in force to which they are exposed by modulating their function. For example, mechanical forces sensed by smooth muscle cells modulate gene expression, protein synthesis, cell morphology, cell proliferation and differentiation. Active and passive force-length behavior of bladder smooth muscle adapts to existing environmental conditions by spatial rearrangement of myosin and actin filaments within the cell, restructuring connections to adhesion plaques that anchor the contractile apparatus to the cell, alteration of the composition of the extracellular matrix or reorganization of bladder smooth muscle cells. However, these adaptive changes have the potential to become pathologic, thus linking remodeled bladder structure with altered mechanical function.

The bladder exhibits marked regional and directional differences in mechanical properties that may reflect heterogeneity in architecture. For example, increased compliance has been observed along the transverse direction relative to the longitudinal direction, promoting horizontal distension during filling. This directional anisotropy may be achieved at a structural level by the orientation of elastin that was observed predominantly in the transverse direction. In addition, regional differences in tensile strength can be attributed to the distribution of collagen, which is especially concentrated in the base of the bladder where tension is greatest.

Region dependent structure-function relationships that are apparent under normal conditions become perturbed with bladder pathology. Structural caveolae, invaginations of

smooth muscle membranes, are decreased in patients with overactive bladder and bladder outlet obstruction, and in the aging bladder. These structural microdomains and their integral membrane proteins, caveolins, play an important role in signaling regulation and serve as membrane reserves to limit increases in cell tension during stretch. We have demonstrated an isoform-specific spatial distribution and distinct molecular interaction of caveolin proteins that contribute to mechanical heterogeneity in bladder smooth muscle and facilitate differential modulation of responses to local stimuli. Distinct contractile responses have been shown in bladder tissue incised from longitudinal and circular directions. Thus, the restricted expression of specific caveolin isoforms to the inner smooth muscle layers of the bladder may provide a molecular basis for regional and directional variability in bladder contractility. The role of caveolin isoforms in defining smooth muscle phenotype may have important implications under disease conditions that cause bladder remodelling in which the orientation and function of bladder smooth muscle cells are markedly altered. For example, previous studies have shown that spinal cord injury causes a shift from a relative predominance of longitudinal over circumferential orientation of bladder smooth muscle cells to an equally bidirectional orientation. As caveolae regulate key signalling processes involved in bladder contraction, altered co-expression profiles of caveolin isoforms may generate a regional imbalance in contraction/relaxation responses, thus leading to bladder dysfunction and impaired voiding behavior.

Clinical Implications of Lower Urinary Tract Biomechanics

Christopher Chermansky, MD

First-line pharmacologic treatment of Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO) involves either oral antimuscarinics or β -3 receptor agonists. Antimuscarinics block competitively the effects of acetylcholine (ACh) at post-junctional M_2 and M_3 receptors. Furthermore, antimuscarinics decrease afferent noise produced from the urothelial release of ACh, through the release of ATP, to improve bladder compliance. Together these effects reduce OAB symptoms without affecting voiding. However, aging produces changes in muscarinic receptors and afferent activity which may decrease detrusor contractility.

β -3 receptor agonists have been shown in experimental human studies to inhibit spontaneous contractile activity in vitro and detrusor overactivity in vivo. Furthermore, mirabegron was shown in rats to reduce the activity of bladder A delta and C fibers during filling to improve bladder compliance. This resulted in an increase in bladder capacity without changes in micturition pressure or residual volume. The North American and European-Australian Phase 3 RCTs of mirabegron in OAB patients showed statistically significant increases in mean volume voided, albeit small, in patients treated with mirabegron compared to placebo.

Treatment of detrusor overactivity (DO) with intradetrusor Botulinum-A neurotoxin (BoNT/A) injections temporarily blocks the presynaptic release of acetylcholine from the parasympathetic innervation of the bladder to produce a paralysis of the detrusor smooth muscle. BoNT/A would temporarily block the presynaptic release of ACh from the parasympathetic innervation and produce a paralysis of the detrusor smooth muscle, comparable to its mode of action in skeletal muscle. However, BoNT/A injections have been shown to increase bladder capacity, volume at first reflex detrusor contraction, and bladder compliance as well as to induce changes in detrusor function with decreases in detrusor pressures during bladder filling and voiding. Ginsberg conducted a Phase 3 RCT of BoNT/A of patients with UUI from NDO. They showed that maximum cystometric capacity increased 151 cc in patients treated with BoNT/A. In another Phase 3 RCT of BoNT/A of patients with UUI

from NDO, Cruz et al showed that maximum cystometric capacity increased 157 cc in patients treated with BoNT/A. These urodynamic changes underlie the remarkable symptomatic improvements in frequency and urge urinary incontinence that patients are reporting. Prominent in patients' clinical responses to BoNT/A is an amelioration in their pathological sensation of urgency, a sensation believed to be afferently mediated. These benefits are maintained for up to a mean of 9–11 months after treatment. Comparable responses have been demonstrated in patients with intractable NDO of various spinal etiologies and in patients with IDO.

An afferent mechanism for botulinum toxin involving a complex interaction between the release of neurotransmitters and actions on respective receptors located on structural constituents suggests that the primary peripheral effect of BoNT/A is the inhibition of release of acetylcholine, ATP, substance P, and reduction in the axonal expression of the capsaicin and purinergic receptors. This may be followed by central desensitization through a decrease in central uptake of substance P and neurotrophic factors.

Sacral neuromodulation is approved for urinary urgency, frequency, urge incontinence and non-obstructive urinary retention in patients who have not been helped or could not tolerate more conventional treatments, including pharmacotherapy. Neuromodulation is thought to work by stimulating somatic afferent fibers, thereby influencing continence and voiding reflex pathways within the spinal cord. Van Kerrebroeck et al published a 5 year prospective multicenter trial of 152 patients that underwent sacral neuromodulation. Of those implanted – 96 had UUI, 31 had retention, and 25 had urgency frequency. For patients with urgency frequency the mean volume voided per void increased from 92 ml to 165 cc ($p < 0.001$). This represented a statistically significant increase in bladder capacity. For patients with non-obstructive urinary retention the mean volume per catheterization decreased from 380 cc to 109 cc ($p < 0.001$). This represented a statistically significant increase in detrusor contractility.

Percutaneous tibial nerve stimulation (PTNS) works to treat bladder overactivity by increasing afferent signaling through the sacral nerve plexus. Tai et al has shown increases in bladder capacity when using tibial neuromodulation to treat cats with bladder overactivity. These results became even more statistically significant when tibial neuromodulation was

combined with tramadol, to within 85% of control. Peters et al performed a RCT comparing 12 weekly 30-minute PTNS sessions to sham in 220 adults with OAB. PTNS was found to be superior to sham in # voids/day, UUI, nocturia, and several QOL measures. Yet, the mean increase in volume voided was 11 ml in the PTNS patients versus 6 ml in the sham patients, $p=0.35$. This implies no significant increase with PTNS alone. More studies are needed to comment on the effects of PTNS on lower urinary tract biomechanics.

References for followup

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