Published in final edited form as:

Curr Bladder Dysfunct Rep. 2017 March ; 12(1): 35–41. doi:10.1007/s11884-017-0407-6.

Pathophysiology of the Underactive Bladder: Evolving New Concepts

Phillip P. Smith¹

¹UConn Center on Aging, UConn Institute of Brain and Cognitive Science, University of Connecticut School of Medicine, Farmington, CT, USA

Abstract

Purpose of Review—Underactive Bladder (UAB) is an emerging concept of voiding dysfunction, building on a tradition of often overlapping and confusing terminologies describing the patient experience, urodynamic function, and pathophysiology. This confusion of symptoms with function with pathology has hampered development of an effective disease model.

Recent Findings—As with other urinary symptoms, the relationship of voiding symptoms to urodynamic dysfunction is variable. Efforts are underway to formally define UAB as a collection of symptoms related to voiding. Defined as voiding symptoms, UAB cannot be reliably linked to detrusor underactivity (DU) nor to detrusor weakness.

Summary—Progress will be made by characterizing the functional disorders underlying UAB symptoms, examining the biology of these linkages, re-conceptualizing urinary control as one part of a more global biologic adaptive physiology, and determining the relationships of central and peripheral pathologies leading to disrupted control mechanisms.

Keywords

Underactive bladder; Voiding dysfunction; Pathophysiology

Introduction

In the past decade, underactive bladder (UAB) has received increasing attention, yet remains elusive in its meaning and connotations. A Pubmed search reveals that the association of the term “underactivity” with bladder voiding performance first appears in the literature in 1980, in an article by Dr. Paul Abrams discussing the etiology of post-prostatectomy voiding difficulties [1] (notably, Dr. Abrams remains one of the leading voices in the UAB world). He described the underactive bladder as urodynamic finding largely paralleling the current definition of “detrusor underactivity (DU).” “Underactive Bladder” first appears in a 2005 nursing review by Rigby [2•], in which UAB is used to describe symptomatic detrusor

Correspondence to: Phillip P. Smith.

Conflict of Interest: Dr. Smith is funded by the CT Institute of Brain and Cognitive Science and these are two separate grants relating to this work. NIA 1K76AG054777-01.

Compliance with Ethical Standard: Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by any of the authors.

underactivity, equating a specific set of symptoms with an objective performance measure. Since then the term has assumed a variety of connotations, all containing the broad implication of impaired voiding. Even within the past year, it has variably been used as a symptom descriptor [3], a statement on bladder function (including as a synonym for DU) [4], and a pathophysiologic concept [5]. This kind of linguistic imprecision risks robbing the term of value. Of 53 publications containing the term “underactive bladder,” the majority (31) are reviews and opinion pieces; lots of smoke, not enough fire, and what exists is complicated by terminologic confusion. Fortunately, in the interests of clarity and hopefully progress in understanding the symptoms of impaired voiding and their causes, both the ICI Research Society [6•] and the International Continence have considered UAB. An Underactive Bladder committee of the ICS is formulating a formal definition (based on expert opinion), to be included in an updated terminology document. The definition regards UAB as the perception of hesitancy, straining to void, difficulties with the stream, incomplete bladder emptying, and (interestingly) reduced sensation of bladder filling—in other words, a symptom complex. This is a useful first step, as it distinguishes UAB as a perception of bladder function from urodynamic quantification of detrusor voiding function, and separates UAB from pathophysiologic concepts linking cellular/molecular mechanisms to function. This review will then focus on a new question, *why do patients experience UAB?*

UAB as a Symptom Complex

Voiding-associated symptoms describing UAB are associated with impaired quality of life, and as severity of UAB symptoms increase, symptoms of frequency, urgency, and incontinence increase in prevalence as well [3]. It is therefore useful to reconsider UAB in the context of the traditional division of bladder function into “urine storage” and “urine voiding.” Normal bladder filling sensations have been formally described as “the individual is aware of bladder filling and increasing sensation up to a strong desire to void [7].” Sensations may be increased, reduced, absent, or atypical. Contained within the ICS [7], statement on normal urine storage sensations is the absence of sensation of bladder filling, interrupted by an increasingly intrusive sensation of desire to void the bladder, sufficient to prompt non-urgent action toward socially appropriate emptying. The perception of disordered urine storage/bladder filling includes frequency/persistence of desire (frequency, nocturia) or suddenness/discomfort (urgency), and is generally described by the term “overactive bladder (OAB).” Symptom-based therapies, derived in the hope of simplifying medical management, include pharmacologic agents aimed at suppressing abnormal detrusor activity (urodynamically quantified as detrusor overactivity, DO) and are outlined in an AUA/SUFU algorithm [8]. Unfortunately, this equation of symptoms with pathology does not mean that available therapies can be expected to be fully effective, well tolerated, and safe. In the elderly, an important group due to a high prevalence of urinary symptoms, available pharmacologic remedies may be more dangerous than beneficial [9, 10], and neuromodulator techniques present potential efficacy and administrative problems [11]. Linking symptoms to urodynamic measurements of bladder storage has not met with satisfactory therapeutic success; DO is neither necessary nor sufficient for OAB [12, 13].

OAB is in fact only a perception of abnormal bladder volume management during storage phase.

Despite much attention to urine storage, normal voiding sensations have not been subject to scientific scrutiny. They would seem to include the absence of discomfort or strain, a typical/expected continuous stream, and a sense of completeness of emptying. The perception of disordered voiding is described by *voiding symptoms* (including intermittency, hesitancy, and slow stream) and *post-micturition symptoms* (sense of incomplete emptying and dribble) [7]. Normal voiding is understood to require intravesical expulsive pressure, resulting from the force of coordinated detrusor myocyte contraction. The balance of pressure and flow is determined by the degree to which the urethra distends in response to this expulsive pressure. Contractile force must be sufficient and durable to maintain urethral opening and therefore flow, ensuring bladder emptying. An insufficiency of strength and/or duration—resulting in prolonged emptying and/or achieve complete bladder emptying within a normal time period—defines detrusor underactivity (DU). It is thus tempting to link symptoms (UAB) with objective function (DU) and therefore to the tissue/cellular/molecular contributors to DU.

The search for treatment of UAB historically and tacitly linked UAB, DU, and detrusor muscle contractile abnormalities despite lack of a demonstrated linkage of perceptions (UAB), function (DU), and detrusor pathophysiology (impaired contractility) [14•]. Previous attempts at pharmacologic therapies have sought to improve the pressure/flow characteristics of voiding, either by enhancing detrusor force production or lowering outlet impedance to flow [15]. Despite decades of research, therapy is still largely limited to catheterization regimens (although neuromodulatory techniques have use in certain cases, but notably not because they are aimed at directly improving the pressure/flow relationship [16–18]).

UAB, DU, and impaired contractility cannot be reliably associated with each other, and UAB is only weakly predictive of the urodynamic finding of DU (Figure 1) [19]. For men and women together, sensitivity and specificity of UAB symptoms for urodynamic DU were 0.22 (0.12–0.35) and 0.90 (0.84–0.94), respectively ($p = 0.04$). Broken down by sex, these associations did not achieve statistical significance. There is no study testing the prevalence of DU in an asymptomatic population, therefore precluding the calculation of predictive values of DU for any symptom complex including UAB, and similarly of UAB for DU in a typical clinic population. Clearly therefore, any therapeutic paradigm that depends upon a firm linkage between detrusor muscle impairment, DU, and UAB could not be expected to routinely yield success.

New therapeutic directions will require a reconsideration of UAB etiology. As was suggested long ago [20, 21], a de-linkage of symptoms/sensations and function as an approach to etiologic/pathophysiologic investigations may be a more useful approach to urinary symptoms. Once underlying pathophysiologic processes are better understood, phenotyping with appropriate statistical testing may allow an eventual effective symptom-based approach. Regarding UAB strictly as a symptom complex, its causes can easily be understood as multifactorial, in the context of aging and concurrent morbidities. Organic contributions on a molecular, cellular, tissue/organ, and system level are variably influenced

by genetics and lifestyle choices. Perceptions of normal function are the result of a successful multi-system adaptation to physiologic challenge. UAB is therefore the perception of an adaptive failure; the perceived full bladder cannot be emptied as expected.

Phenotyping UAB

Perception may or may not reflect a functional reality, and expectations are ultimately subjective. Normal voiding is the voluntary event terminating a low-pressure storage phase punctuated by typical sensations of bladder volume as the bladder fills. Efficient emptying (small post-void residual volumes) of normal volumes with age-appropriate flow rates constitute constitutes an accepted norm [22–26], although diminished flow rates and higher PVRs are observed in asymptomatic older individuals [27–29]. Flow rates falling below normative values and elevated PVRs should not be regarded as UAB in the absence of voiding-associated symptoms, even though these findings may be necessary considerations in the otherwise symptomatic patient. Similarly, UAB symptoms in the absence of age-adjusted abnormalities of storage or voiding should prompt inquiry into a perceptual etiology, rather than a further search for genitourinary dysfunction. Furthermore, the use of the term UAB implies that the patient suffers the symptom; those who care for the incapacitated may report incomplete bladder emptying or flow, which should not be considered UAB as the patient does not report these symptoms.

The cause of UAB in the cognitively intact patient ultimately relates to impaired bladder volume management. At this writing, there are no published data to allow functional phenotyping of patients with UAB, yet it is clear that UAB often is the result of factors beyond detrusor muscle failure. Patients with UAB having urodynamic findings consistent with DU could not be classified according to presence or risk of cardiovascular disease, neurologic etiology, or “idiopathic” [30]. Patients reporting voiding symptoms consistent with UAB have higher volume sensory thresholds and PVRs compared to non-UAB patients, but UAB is not associated with impaired contractility [19]. Sensory, central control, and detrusor motor factors must all be considered [6•].

Table 1 presents an UAB etiologic classification. Linkages to urodynamic function and cellular/tissue-level pathophysiologic mechanisms are inferred. Aging, concurrent disease, and injury (such as stroke, closed head trauma, or vertebral fracture) can be seen as risk factors for these mechanisms. This categorization is not to suggest that any individual case can be slotted into one subheading; especially in later life, many of these factors likely are co-operational.

The perception of lower urinary tract dysfunction (LUTD) can first be considered to be correct or incorrect: a “correct” perception links symptoms to an LUT dysfunction (although not necessarily DU), whereas an incorrect perception links an extravesical problem to vesical symptoms. In the absence of demonstrable storage or voiding dysfunction, excessive demands on LUT function by polyuria or perceptual disorders due to dementia or psychiatric illness may yield the perception of UAB; this is an “incorrect” perception. The correct perception of LUT dysfunction identified as UAB can be further divided into “accurate” vs. “inaccurate” perceptions. A voiding phase disorder producing impaired stream and/or an

elevated PVR is accurate, whereas UAB in the absence of a slow volume/age-adjusted stream and/or elevated residual volume is inaccurate. For example, patients with volume hypersensitivity with or without detrusor overactivity may perceive an inability to further empty the already-empty bladder and/or a diminished flow associated with small volume voids and therefore meet the criteria of UAB. A common example of this phenomenon is often seen in the otherwise healthy female patient with a UTI. Less commonly, massive vesicoureteral reflux or a large bladder diverticulum leads to expansion of the urinary reservoir beyond the detrusor-bounded bladder. Volume contained within a noncontractile bladder extension and dissipation of detrusor forces into further expansion of this non-detrusor-bounded bladder could impair voiding, yielding a slow stream and/or incomplete emptying (the resulting elevated postvoid residual from rapid refill could further complicate the diagnostic evaluation in the absence of imaging!). The perception is correct—there is a bladder problem—but it is inaccurate since the real defect lies with a storage defect.

The correct and accurate perception of a voiding disorder yields symptoms of impaired voiding and/or incomplete emptying, i.e., UAB. An objective voiding disorder is the result of a disordered pressure/flow relationship. This can be broadly parsed into the nonexclusive categories of detrusor underactivity (DU) and an impaired outlet function.

The etiologies of DU have been classified as myogenic vs. neurogenic [14•]; however, this divide may be artificial. The etiology of DU may be a disorder of bladder volume sensitivity (hyposensitivity during filling) [31, 32]. Volume sensory transduction is postulated to initiate with the non-neuronal release of neurotransmitters from the urothelium, acting on suburothelial components resulting in the generation of afferent activity directly related to both volume and the volume-induced tensions in the bladder wall [33–36]. Autonomous detrusor myocyte activity, modulated by autonomic input, contributes to this tension, resulting in so-called afferent noise [37, 38]. Animal models suggest that parasympathetic stimulation may augment these tensions—and therefore the afferent data stream—as a voiding threshold volume is approached [39]. The decentralized bladder loses capacity and compliance suggesting central regulatory input via sympathetic innervation allows for both low-pressure storage and downward regulation of afferent sensitivity to volume [40–43]. Thus, factors that affect the relationship of tension to volume are all potential etiologies of volume sensitivity disorders.

In general, these factors pertain to the extracellular matrix (a passive “spring element”) and the determinants of detrusor myocyte activity and coordination among the myocytes (“contractile” or “motor” element) [44, 45]. Congenital and disease-induced alterations in the structure, content, and metabolism of collagens [46–51] could be expected to yield disordered passive contributions which, even in the face of normal myocyte action, could alter the normal tension/volume relationship as the bladder fills [52] and thus, distort the relationship of afferent activity to volume as the bladder fills; it is possible that central mechanisms could provide adaptive regulation of myocyte activity; however, these may be less capable in the same populations (e.g., the aged) likely to suffer altered structure. Similarly, despite normal passive elements, dysregulation of detrusor myocyte activity and/or coordination during filling could exceed adaptive capabilities and result in dysfunctional sensory abnormalities [38]. As demonstrated with $\beta 3$ agonists, if activity is

suppressed, afferent activity becomes less sensitive to increasing volume [53]; carried to a pathologic degree, this mechanism could contribute to DU and thus UAB.

Mechanisms which could contribute to an abnormal motor element—either indirectly via maladaptive sensory processes leading to impaired efferent outflow or directly via insufficient responsiveness to parasympathetic drive—include myocyte pathology (inherent myopathies, mitochondrial disease, defects in Ca^{++} handling), loss of myocytes, and impaired coordination of myocyte activity. The flaccid yet insensate bladder of the diabetic with voiding complaints/UAB suggests disease-induced loss of tension-inducing autonomous myocyte activity and resultant afferent noise, either due to disease-induced myopathy or intercellular signaling within the urothelium/lamina propria/detrusor complex. Neurologic factors affecting detrusor motor voiding function include insufficient efferent drive due to neuropathy or impaired central parasympathetic outflow. Loss of central responsiveness to bladder volume (as observed with advancing age [54]) [54]), due to either impaired volume transduction, loss of spinal transmission, or aberrant cortical responses, can contribute to loss of adaptive sympathetic regulation of bladder filling and initiation/maintenance of a pontine voiding reflex. The success of neuromodulation in both normalizing brain responses and in addressing the severe UAB characterized as Fowler's syndrome [17, 55, 56] supports this linkage of sensory abnormalities with UAB.

Poor urethral distensibility can contribute to UAB despite normal detrusor pressure generation. The causes of outlet obstruction do not require elaboration here, but it is worthwhile to note that dysfunctional voiding (“non-neurogenic neurogenic bladder”) can be obstructive (as in Hinman's or Fowler's syndrome), incorporate a potentially etiologic element of sensory pathology, and reflexly suppress detrusor output. Relatively fixed obstructions such as posterior urethral valves, stricture, prior incontinence operations, and BPH can also lead to bladder wall inflammation, denervation, fibrosis, and sarcopenia, all leading to a mix of both motor and sensory elements in the oft-resulting detrusor insufficiency as well as impaired bladder emptying characterizing UAB. The distinction between DU and obstruction is often blurred [57], and while both are certainly contributors to UAB, the degree to which UAB—alone or in combination with non-invasive objective measures—can be used to distinguish these pathologies has not been reported.

Conclusions

UAB is defined as a voiding symptom complex suggesting the urodynamic observation of DU. Just as DU does not correlate well with impaired detrusor contractility, neither does UAB correlate well with DU. Overlapping functional disorders resulting from multiple congenital, age-, and disease-induced pathophysiologic processes yield the perception of hesitancy, slow stream, and incomplete emptying. An etiologic categorization is suggested. Early research goals should include improvement and validation of a categorization scheme, subject to modification as a knowledge base develops. From there, specific pathophysiologic processes can be identified and researched on a basic science level, with translational/clinical research working to identify the markers which could yield a correct functional categorization of individual patients. Meaningful population studies and selection of relevant therapeutic targets would then contribute to improved evaluation and management of UAB.

The evaluation and post-palliative management of UAB requires more than a search for a “magic bullet.” An integrative approach is needed, including sensory and motor functions, and central and lower urinary tract capabilities and interactions.

References

Papers of particular interest, published recently, have been highlighted as: • Of importance

1. Abrams PH. Investigation of postprostatectomy problems. *Urology*. 1980; 15(2):209–12. [PubMed: 7355551]
- 2•. Rigby D. Underactive bladder syndrome. *Nurs Stand*. 2005; 19(35):57–64. Quiz 66–7. It is a statement on the general lack of progress in this area that the Rigby review remains generally timely.
3. Faraj K, et al. A cross-sectional study in the USA of the epidemiology and quality of life of underactive bladder symptoms. *Int Urol Nephrol*. 2016; doi: 10.1007/s11255-016-1382-0
4. Liu Z, et al. Underactive and overactive bladders are related to motor function and quality of life in Parkinson's disease. *Int Urol Nephrol*. 2015; 47(5):751–7. [PubMed: 25792006]
5. Sekido N, et al. Promising effects of a novel EP2 and EP3 receptor dual agonist, ONO-8055, on neurogenic underactive bladder in a rat lumbar canal stenosis model. *J Urol*. 2016; 196(2):609–16. [PubMed: 26880410]
- 6•. Smith PP, et al. Detrusor underactivity and the underactive bladder: symptoms, function, cause—what do we mean? ICI-RS think tank 2014. *Neurourol Urodyn*. 2016; 35(2):312–7. The definition of UAB has been amorphous in the past, leading to confusion of symptoms, dysfunction, and etiology. Recent efforts towards a formal definition are leading to UAB as a description of symptoms, i.e., the patient's experience of voiding dysfunction. No specific objective dysfunction or causative pathophysiology should be inferred. By permitting comparative phenotyping between symptoms and function, this emerging formalization of UAB as a symptom complex will contribute to scientific progress. [PubMed: 26872574]
7. Abrams P, et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002; 21(2):167–78. [PubMed: 11857671]
8. Gormley EA, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*. 2012; 188:2455–63. American Urological Association (AUA) Guidelines. [PubMed: 23098785]
9. Moga DC, et al. Risks and benefits of bladder antimuscarinics among elderly residents of Veterans Affairs Community Living Centers. *J Am Med Dir Assoc*. 2013; 14(10):749–60. [PubMed: 23639715]
10. Pagoria D, O'Connor RC, Guralnick ML. Antimuscarinic drugs: review of the cognitive impact when used to treat overactive bladder in elderly patients. *Curr Urol Rep*. 2011; 12(5):351–7. [PubMed: 21607875]
11. Griebing T. Sacral nerve stimulation in the elderly. *Int Urogynecol J*. 2010; 21:485–9.
12. Resnick NM, Elbadawi A, Yalla SV. Age and the lower urinary tract: what is normal? (Abstract). *Neurourol Urodyn*. 1995; 14:577–9.
13. Sekido N, et al. How many uncomplicated male and female overactive bladder patients reveal detrusor overactivity during urodynamic study? *Int J Urol*. 2006; 13(10):1276–9. [PubMed: 17010004]
- 14•. Tyagi P, et al. Pathophysiology and animal modeling of underactive bladder. *Int Urol Nephrol*. 2014; 46(Suppl 1):11–21. This is a recent review of pathophysiologic ideas underlying principally detrusor underactivity. Included are ideas how these might relate to UAB as a symptom complex.
15. Smith PP, et al. Advanced therapeutic directions to treat the underactive bladder. *Int Urol Nephrol*. 2014; 46(Suppl 1):S35–44. [PubMed: 25238893]

16. Blok BF, et al. Different brain effects during chronic and acute sacral neuromodulation in urge incontinent patients with implanted neurostimulators. *BJU Int.* 2006; 98(6):1238–43. [PubMed: 17034500]
17. Dasgupta R, et al. Changes in brain activity following sacral neuromodulation for urinary retention. *J Urol.* 2005; 174(6):2268–72. [PubMed: 16280802]
18. Kavia R, et al. A functional magnetic resonance imaging study of the effect of sacral neuromodulation on brain responses in women with Fowler's syndrome. *BJU Int.* 2010; 105(3): 366–72. [PubMed: 19735259]
19. Smith PP, et al. Underactive bladder and detrusor underactivity represent different facets of volume hyposensitivity and not impaired contractility. *Bladder.* 2015; 2(2):e17.
20. Bates CP, Whiteside CG, Turner-Warwick R. Synchronous cine-pressure-flow-cystourethrography with special reference to stress and urge incontinence. *Br J Urol.* 1970; 42(6):714–23. [PubMed: 5491923]
21. Blaivas JG. The bladder is an unreliable witness. *Neurourol Urodyn.* 1996; 15(5):443–5. [PubMed: 8857612]
22. Gaum LD, et al. Age related flow rate nomograms in a normal pediatric population. *Acta Urol Belg.* 1989; 57(2):457–66. [PubMed: 2763925]
23. Toguri AG, Uchida T, Bee DE. Pediatric uroflow rate nomograms. *J Urol.* 1982; 127(4):727–31. [PubMed: 7069841]
24. Gupta DK, Sankhwar SN, Goel A. Uroflowmetry nomograms for healthy children 5 to 15 years old. *J Urol.* 2013; 190(3):1008–13. [PubMed: 23538243]
25. Siroky MB, Olsson CA, Krane RJ. The flow rate nomogram: I. Development. *J Urol.* 1979; 122(5): 665–8. [PubMed: 159366]
26. Haylen BT, et al. Maximum and average urine flow rates in normal male and female populations—the Liverpool nomograms. *Br J Urol.* 1989; 64(1):30–8. [PubMed: 2765766]
27. Jorgensen JB, et al. Uroflowmetry in asymptomatic elderly males. *Br J Urol.* 1986; 58(4):390–5. [PubMed: 3756408]
28. Huang AJ, et al. Clinical significance of postvoid residual volume in older ambulatory women. *J Am Geriatr Soc.* 2011; 59(8):1452–8. [PubMed: 21806559]
29. Pfisterer MH, et al. Parameters of bladder function in pre-, peri-, and postmenopausal continent women without detrusor overactivity. *Neurourol Urodyn.* 2007; 26(3):356–61. [PubMed: 17285577]
30. Brown ET, et al. Phenotyping women with detrusor underactivity by presumed etiology: is it plausible? *Neurourol Urodyn.* 2016; doi: 10.1002/nau.23079
31. Smith PP, Chalmers DJ, Feinn RS. Does defective volume sensation contribute to detrusor underactivity? *Neurourol Urodyn.* 2015; 34(8):752–6. [PubMed: 25220925]
32. Smith PP. Aging and the underactive detrusor: a failure of activity or activation? *Neurourol Urodyn.* 2010; 29(3):408–12. [PubMed: 19760756]
33. Birdler LA. Urothelial signaling. *Auton Neurosci.* 2010; 153(1-2):33–40. [PubMed: 19666243]
34. Kanai A, et al. Origin of spontaneous activity in neonatal and adult rat bladders and its enhancement by stretch and muscarinic agonists. *Am J Physiol Ren Physiol.* 2007; 292(3):F1065–72.
35. Kanai AJ. Afferent mechanism in the urinary tract. *Handb Exp Pharmacol.* 2011; 202:171–205.
36. le Feber J, van Asselt E, van Mastrigt R. Afferent bladder nerve activity in the rat: a mechanism for starting and stopping voiding contractions. *Urol Res.* 2004; 32(6):395–405. [PubMed: 15517231]
37. Gillespie J, et al. On the origins of the sensory output from the bladder: the concept of afferent noise. *BJU Int.* 2009; 103(10):1324–33. [PubMed: 19344428]
38. Gillespie JI. The autonomous bladder: a view of the origin of bladder overactivity and sensory urge. *BJU Int.* 2004; 93(4):478–83. [PubMed: 15008713]
39. Sasaki M. Bladder motility and efferent nerve activity during isotonic and isovolumic recording in the cat. *J Physiol.* 1998; 510(Pt 1):297–308. [PubMed: 9625886]
40. Smith PP, Deangelis AM, Kuchel GA. Evidence of central modulation of bladder compliance during filling phase. *Neurourol Urodyn.* 2012; 31(1):30–5. [PubMed: 22038779]

41. Wein AJ, et al. Sympathetic innervation and chemical sympathectomy of canine bladder. *Urology*. 1974; 4(1):27–32. [PubMed: 21322978]
42. Wein AJ, et al. Effect of long-term chemical sympathectomy on function of canine urinary tract. *Urology*. 1975; 6(2):200–4. [PubMed: 1170670]
43. Vaughan C, Satchell P. Rate of bladder distension and hypogastric nerve activity in the cat. *J Auton Nerv Syst*. 1991; 34(2-3):129–37. [PubMed: 1918806]
44. Coolsaet B. Bladder compliance and detrusor activity during the collection phase. *Neurourol Urodyn*. 1985; 4(4):263–73.
45. Coolsaet BL, et al. Viscoelastic properties of bladder wall strips. *Investig Urol*. 1975; 12(5):351–6. [PubMed: 1112665]
46. Metcalfe PD, et al. Bladder outlet obstruction: progression from inflammation to fibrosis. *BJU Int*. 2010; 106(11):1686–94. [PubMed: 20590549]
47. Rubinstein M, Sampaio FJ, Costa WS. Stereological study of collagen and elastic system in the detrusor muscle of bladders from controls and patients with infravesical obstruction. *Int Braz J Urol*. 2007; 33(1):33–9. discussion 39–41.
48. Sartori MG, et al. Quantitative evaluation of collagen and muscle fibers in the lower urinary tract of castrated and under-hormone replacement female rats. *Clin Exp Obstet Gynecol*. 2001; 28(2):92–6. [PubMed: 11491384]
49. Susset JG, et al. Collagen in 155 human bladders. *Investig Urol*. 1978; 16(3):204–6. [PubMed: 711413]
50. Uvelius B, Mattiasson A. Detrusor collagen content in the denervated rat urinary bladder. *J Urol*. 1986; 136(5):1110–2. [PubMed: 3773079]
51. Yang L, et al. Imbalance between matrix metalloproteinase-1 (MMP-1) and tissue inhibitor of metalloproteinase-1 (TIMP-1) contributes to bladder compliance changes in rabbits with partial bladder outlet obstruction (PBOO). *BJU Int*. 2013; 112(4):E391–7. [PubMed: 23305285]
52. Stevenson K, et al. Functional changes in bladder tissue from type III collagen-deficient mice. *Mol Cell Biochem*. 2006; 283(1-2):107–14. [PubMed: 16444592]
53. Aizawa N, Homma Y, Igawa Y. Effects of mirabegron, a novel beta3-adrenoceptor agonist, on primary bladder afferent activity and bladder microcontractions in rats compared with the effects of oxybutynin. *Eur Urol*. 2012; 62(6):1165–73. [PubMed: 22981677]
54. Griffiths DJ, et al. Cerebral control of the lower urinary tract: how age-related changes might predispose to urge incontinence. *NeuroImage*. 2009; 47(3):981–6. [PubMed: 19427909]
55. De Ridder D, Ost D, Bruyninckx F. The presence of Fowler's syndrome predicts successful long-term outcome of sacral nerve stimulation in women with urinary retention. *Eur Urol*. 2007; 51(1):229–33. discussion 233–4. [PubMed: 16860462]
56. Kavia R, et al. A functional magnetic resonance imaging study of the effect of sacral neuromodulation on brain responses in women with Fowler's syndrome. *BJU Int*. 2009; 9999
57. Oelke M, et al. Unravelling detrusor underactivity: development of a bladder outlet resistance-bladder contractility nomogram for adult male patients with lower urinary tract symptoms. *Neurourol Urodyn*. 2015; 35:980–6. [PubMed: 26235823]

Figure 1.

Contingency table testing association of UAB (symptoms), DU (detrusor voiding function), and impaired contractility (by Watts factor; WFmax = 3.7 is one SD below mean, and WF = 4.7 is lower quartile) in a routine urodynamic population of 56 males and 142 females.

Neurogenic patients and patients unable to void excluded. There is no statistically significant association among UAB, DU, and impaired contractility

Table 1
Underactive bladder: potential etiologic categories

Potential etiologic categories	
A. Correct perception: a storage/voiding dysfunction exists	
a. Accurate perception of abnormal stream and/or PVR	
i. Detrusor underactivity	
1. Myopathy	
a. Cellular	
i. Mitochondrial defects	
ii. Ca++ handling	
iii. Channelopathies	
b. Structural	
i. Connective tissue defects	
1. Fibrosis	
2. Hyperdistensibility	
ii. Diverticulae, VUR	
2. Non-myopathic motor dysfunction	
a. Inappropriate detrusor motor demand	
i. Poor urethral distensibility/outlet obstruction	
ii. Dyssynergic voiding (non-neurogenic)	
b. Insufficient substrate delivery	
i. Vascular insufficiency/systemic	
ii. Vascular insufficiency/local - overdistension	
3. Impaired efferent drive	
a. Loss of efferent pathways	
i. Neurologic disease	
ii. Injury	
b. Impaired pontine de-suppression/voiding launch	
i. Central volume hyposensitivity	
ii. Volume transduction defect	
iii. Impaired cognition	
c. Premature turn-off of efferent voiding drive	
i. Central volume hyposensitivity	
1. Disease (e.g., Parkinson's, MSA)	
2. Trauma (e.g., CVA, TBI)	
ii. Volume transduction defect	
1. Myopathy	
2. Detrusor dysregulation	
3. Autonomopathy	
4. Neuropathy	

Potential etiologic categories	
iii. Impaired cognition	
1. Homeostenosis	
2. Executive function impairment	
3. Dementia	
ii. Poor urethral distensability	
1. Fixed obstruction	
2. Functional obstruction	
b. Inaccurate perception—normal stream, small PVR	
i. Volume hyposensitivity/large pre-void volumes	
1. Central	
a. Disease (e.g., Parkinson's, MSA)	
b. Trauma (e.g., CVA, TBI)	
2. Peripheral/volume transduction defect	
3. Regulatory/impaird cognition	
ii. Volume hypersensitivity/small pre-void volumes	
iii. Detrusor overactivity	
B. Incorrect perception: no objective storage/voiding dysfunction	
a. Perceptual disorder	
b. Polyuria	
i. Organic/renal disease, heart disease	
ii. Iatrogenic—diuretics	
iii. Psychogenic/lifestyle	