Original Article

The role of detrusor rigidity in the lower urinary tract dysfunction. Hypothesis

MICHAEL D. LEVIN

State Geriatric Center, Netanya, Israel

Abstract: Objective. To define the role of detrusor rigidity in the pathogenesis of various forms of low urinary tract dysfunction. *Results*. We hypothesize that the motility of the urinary system and anorectal zone are subject to the same laws. Extrapolating the known mechanisms of fecal continence and defecation to urination, we propose a hypothesis of motor function of the lower urinary system. Changes in voiding parameters in lower urinary tract dysfunction (LUTD) suggest that detrusor contractility and efficiency decrease with age. This is characterized by a decrease in volume of the urinary bladder, and the thickening of its wall. Smooth muscle fibers are gradually replaced by connective tissue, leading to loss of elasticity and hence increased rigidity of the detrusor. Similar changes occur in the urethral sphincters. Contraction of the prostate then acts to support urinary retention in men when urination is delayed for long periods. In patients experiencing LUTD, it strikes more frequently at night than during the daytime. In this paper we discuss the mechanisms of pathological change as a result of the detrusor rigidity from the detrusor overactivity to the bladder outlet obstruction and then to the underactive detrusor are discussed. *Conclusion:* Taken in conjunction with the concept of age related rigidity of the detrusor and urethral sphincters, our proposed hypothesis of lower urinary tract motility allows us to view the pathogenesis of various impairments of urination as a single process. This makes it possible to explain all the symptoms of LUTD. Further testing of the hypothesis is necessary.

Keywords: Hypothesis; Physiology of urination; Prostate; Rigidity; Urodynamic dysfunction; Urethral sphincters.

Abbreviations:
BPH – benign prostatic hypertrophy; LUTS – lower urinary tract symptoms;
BOO – bladder outlet obstruction; DO – detrusor overactivity;
DU – detrusor underactivity; LUTD - lower urinary tract dysfunction;
IAP – intra-abdominal pressure; TP-1 - threshold pressure-1 (filling);
TP-2 - threshold pressure-2 (urge); TP-3 - threshold pressure-3 (urgency);
IUS – internal urethral sphincter; EUS – external urethral sphincter;
PRM – puborectalis muscle.

INTRODUCTION

According to the International Continence Society's 2002 standards lower urinary tract symptoms (LUTS) can be divided into three groups: storage symptoms (increased daytime frequency, nocturia, urgency, urinary incontinence); voiding symptoms (slow stream, splitting or spraying, intermittent stream, hesitance, straining, terminal dribble); and postmicturition symptoms (feeling of incomplete emptying, post micturition dribble)[1]. On the basis of urodynamic studies of patients where acute and chronic prostatitis, neurological diseases, urethral stricture or injury, and surgeries are excluded, the following syndromes are diagnosed: bladder outflow obstruction (BOO), detrusor overactivity (DO) and detrusor underactivity (DU)[1,2].

Most men eventually develop histological benign prostatic hypertrophy (BPH) if they live long enough. Approximately half develop benign prostatic enlargement, and about half of these cases develop BOO with high bladder pressures and low flow, which in turn leads to detrusor wall hypertrophy. Many of these men only have LUTS, but a significant number also suffer complications from BPH[3]. While many men develop increased outlet resistance with aging as a result of prostatic hypertrophy, no anatomic corollary exists in women. It has been shown that female detrusor contractility and effectiveness decrease with age[4]. The common symptoms of voiding dysfunction in older women - such as a slow urine stream, straining to void, a feeling of incomplete bladder emptying, need to re-void and position-dependent micturition - do not differ much from symptoms in older men, except in cases with BOO[1-4].

Condition of the bladder wall in LUTD

The ultrastructure of the detrusor corresponds perfectly to its urodynamic behavior with time[5]. In control patients the detrusor muscle bundles were composed of smooth muscle cells closely packed together with very little intervening connective tissue. In contrast, and irrespective of age, in patients with prostatic hypertrophy, detrusor muscle from trabeculated bladders were found to contain many muscle bundles in which the constituent cells were of relatively small diameter and were widely separated from each other by dense masses of connective tissue[6].

Ultrasound measurement of bladder wall thickness showed a highly significant association with DO[7,8,9]. Studies of autonomous bladder micromotions in urinary storage and voiding showed that in LUTS, efferent control of the bladder can be impaired due to peripheral "patchy" denervation. This impairs regulation of micromotility initiation and propagation, potentially allowing the emergence of an overactive bladder and, with progression DO[10]. In the elderly, the main alteration in voiding function is due to higher prevalence of DO. Despite the increased prevalence of DO, detrusor contractility declines with age. This may be due to age-related changes in detrusor muscle function, urethral function and sensory function[11]. When detrusor specimens from elderly subjects with impaired contractility were examined by electron microscopy, they displayed widespread degeneration of muscle cells and axons[12]. Biological aging significantly decreases bladder smooth muscle caveolae number and morphology, with associated selective alteration in caveolin protein expression. Since caveolae are protected membrane regions that regulate signal transduction, age-related alteration in caveolae and caveolin protein expression could alter bladder smooth muscle contractility, resulting in bladder dysfunction in the elderly[13].

In BOO the pattern was characterized by widely separated muscle cells with reduction of intermediate cell junc-

tions, collagenosis, (i.e. abundant collagen plus some elastic fibers) in the markedly widened spaces between individual muscle cells, and abundant profiles characteristic of enlarged, hypertrophic muscle cells. Features of a myohypertrophy pattern, with or without superimposed degeneration, can explain the overall weakness of the obstructed detrusor despite hypertrophy of its cells[12].

Bladder function in LUTD

Changes in the structure, metabolism and innervation of the bladder may occur with BOO and with aging itself. These changes lead to voiding dysfunction, but it is difficult to distinguish the effect of BOO from those of aging, since both can trigger similar pathological processes and outcomes[14]. Cystometric parameters have revealed a significant age-related decrease in bladder capacity ($p<0.001$) and bladder compliance ($p=0.004$). Pressure flow study has revealed a significant decrease in voiding efficiency ($p=0.029$), and voided volume ($p<0.001$)[15]. The study of Mori et al. indicates that 15 month matured rats exhibit bladder overactive and underactive conditions as evidenced by increased non-voiding contraction and decreased maximum voiding pressure with increased residual volume, respectively[16].

Prostate

Benign prostatic hyperplasia (BPH) is fundamentally a histologic diagnosis that refers to a non-malignant proliferative process of the cellular elements of the prostate. It usually begins as a simple micronodular hyperplasia with a subsequent macroscopic nodular enlargement that may result in BOO and the development of LUTS. As the prostate enlarges, it constricts the urethra, inducing various symptoms such as: weak urinary stream, incomplete bladder emptying, nocturia, dysuria, and BOO[17]. Although LUTS are associated with urinary flow and prostate size, there is substantial evidence that men can have symptoms even in the absence of BPH, enlarged prostate on physical examination, or abnormal urinary flow rates. This is partly because LUTS can be caused by multiple mechanisms, including prostate and bladder smooth muscle tone and contractility. Moreover, the prevalence of LUTS in women is not too dissimilar to that in men[18].

DISCUSSION

We analyze the different forms of urinary tract dysfunction in light of our proposed hypothesis of lower urinary tract motility[19].

Normal lower urinary tract motility – a hypothesis.

Based on the assumption that all peristaltic organs obey the same laws, we offer a hypothesis of the motor function of the lower urinary tract. In an empty bladder the pressure on its wall is equal to the intra-abdominal pressure (IAP). The accumulation of urine in the bladder occurs at a constant pressure – threshold pressure of the 1st order (TP-1), which is slightly higher than IAP. When urine volume reaches 300-400 ml (the main volume), the pressure in the bladder is increased to the threshold pressure of the 2nd order (TP-2), which causes relaxation of the internal urethral sphincter (IUS). Urine penetrating to the neck of bladder stimulates the urge to urinate. At this moment, retention of urine is provided by the contraction of the external urethral sphincter (EUS) and puborectalis muscle (PRM). If urination is not possible, the detrusor relaxes, adapting to the new volume and intravesical pressure decreases from TP-2 to TP-1, which leads to a reflex contraction of IUS and passive relaxation EUS and PRM. Inflow to the bladder of an additional urine volume again causes an increase in pressure to TP-2, following by relaxation of the IUS and contraction of the EUS and PRM. While the EUS and PRM contract, the IUS relaxes to recover its contractile capacity and vice versa. This ensures continued retention of urine. Urination begins with tension of the abdominal wall, which causes an increase in intra-abdominal pressure and an increase in pressure in the bladder from TP-2 to TP-3. All sphincters (IUS, EUS, and PRM) relax, and the urine under pressure flows through the opened urethra as the result of coordinated contraction of the bladder micromodules. The maximum volume of urine after a long delay can be up to 1 liter (including the main and reserve volume, which enters the bladder as the result of forced delay). In the event of a bladder overflow, the prostate plays a role in the retention of urine. When the volume in the bladder exceeds the main plus reserve volume, the arrival of a new portion of urine does not cause relaxation of the bladder; instead the bladder pressure rises to TP-3, which leads to the reflex contraction of the prostate.

Pathophysiology of lower urinary tract dysfunction. A hypothesis

Drake believes that the basic functional unit of the detrusor is a circumscribed area of muscle known as a module. In the right circumstances, each module can contract independently. Activity in neighbouring modules can be co-ordinated so that a large proportion of the bladder wall becomes synchronously active. In detrusor overactivity, the modules are abnormally active and closely co-ordinated[20]. In a further article, Drake and colleagues argue that in this "... impairs regulation of micromotility initiation and propagation, potentially allowing emergence of overactive bladder and, with progression, detrusor underactivity"[21]. This well-known phenomenon of the combination of decreasing detrusor contractility and bladder overactivity in the elderly does not have a convincing explanation. There is no apparent logic to the combination. If detrusor contractility declines with age, how could it lead to the bladder being overactive?

On the basis of clinical studies and animal models, age-related changes in bladder function have been found in both sexes. Time of onset of symptoms and their severity depends on genetic predisposition and risk factors (gender differences, atherosclerosis and oxidative stress)[22]. Age-related changes in the bladder wall are characterized by the presence of a myohypertrophy pattern, with or without superimposed degeneration, with an increased volume of connective tissue. This can explain overall weakness of the detrusor despite hypertrophy of the bladder wall. As a result of these changes the wall of the bladder loses its elasticity, i.e. becomes more rigid. This stops the bladder stretching and accommodating normal main and reserve volumes of urine, and causes the force of its contraction during urination to be significantly weakened. Age-related rigidity of the bladder helps explain the significant decrease in voided volume, decrease in bladder capacity and compliance, and decrease in voiding efficiency.

Despite the change in some parameters, we have assumed that all the basic laws of lower urinary tract motility in elderly patients remain the same as in controls. In healthy volunteers small-volume vesical distention effected no significant urethral or vesical pressure changes, while distention with 350 and 400 ml of saline produced elevated vesical pressure and decreased urethral pressure[23]. On our view, 350-400 ml of fluid exceeds the basic volume; as a result the bladder ceases to relax and the bladder pressure

rises from TP-1 to TP-2. In DO a urine volume of 100-150-250 ml (it is different in each case) causes a rise in bladder pressure, because after its introduction into the bladder the rigid wall is no longer able to relax and intravesical pressure rises from the TP-1 to TP-2. We therefore believe that age-related changes in the bladder wall, which are similar to the changes occurring in other tissues of the body, lead to rigidity of the wall and LUTD.

Bearing in mind the significance of tissue rigidity, and on the basis of our proposed hypothesis of normal physiology of the lower urinary tract, it is possible to explain all forms of LUTD.

"Detrusor overactivity"

The rigidity of the detrusor is caused by degeneration of muscle cells and axons and peripheral "patchy" denervation of micromodules. This chronic progressive process causes increased collagen deposition and decreased elasticity. As a result, there is a weakening of the contractions, and a discoordination of the contractions of different modules during voiding.

Storage symptoms: Since the main volume of the bladder is reduced to 150-200 ml, compared to 400 ml in normal bladders, with normal given daily volume of urine the *frequency of urination increases*. *Nocturia* differs from daytime urination only in that the intervals between voiding can be longer, since the subject waking depends on the depth of sleep. *Urgency* is a symptom of a more severe degree of rigidity of the bladder wall, when the reserve volume of the bladder approaches zero. In such cases, after raising the intravesical pressure from TP-1 to TP-2, the pressure rises rapidly to TP-3. This state easily changes into *urinary incontinence*, which also depends on changes in sphincter function.

Voiding symptoms: A *slow stream* is the result of weakening contractions and discoordination of the contractions of the different modules, which does not exclude the possibility of narrowing of the urethra. A rigid detrusor is not able to maintain the stability of intravesical pressure. When the pressure is reduced from TP-3 to TP-2 during urination, a reflex contraction of EUS arises. This natural, but not paradoxical contraction of EAS leads to the termination of urination. Gradually, the pressure rises to TR-3 and urination resumes - bringing *symptoms of intermittent stream*, hesitance and straining. A *terminal dribble* is the result of sphincter weakness. In this way, the symptoms of intermittent stream and detrusor sphincter dyssynergia are explained. Rigidity of the bladder therefore explains the pathogenesis of the symptoms of *post-void residual volume*.

We suggest that age-related changes in the bladder wall, which are similar to the changes occurring in other body tissues, lead to rigidity of that wall and hence to LUTD. Similar changes take place in the IUS, which is a thickened continuation of the bladder wall, as well as in the EUS and PRM. A rigid EUS relaxes during urination, but its inner lumen, i.e., urethral diameter, is not returned to normal. Narrowing of the urethral lumen causes resistance to urinary flow, which leads to increased intravesical pressure and a slow urinary stream. Rigidity in the EUS is manifested not only in partial relaxation of the urethra during voiding, but also by weak sphincter contraction during storage, which is the reason for dribbling.

Bladder outlet obstruction

The main and reserve volume gradually decrease due to rigidity of the detrusor. This means that the time between the first desire to void (TP-2) and urgency (TP-3) arising becomes shortened. Since intravesical pressure rises to TP-3 with smaller amounts of urine, it happens more frequently than normal, both at night and during the day. In men, every time the pressure rises to more than TP-3 (overflow), prostate contraction takes place to aid urinary retention. The prostate contracts more often not only at night, but also in the daytime. This frequent contraction of the prostate is the reason for its hypertrophy.

Thus, a vicious circle arises. Age-related changes lead to rigidity of the tissues and more frequent contraction of the prostate, which causes the development of prostatic hypertrophy and narrowing of the urethral lumen. This causes an increase in intravesical pressure, hypertrophy and rigidity of the bladder wall.

The pathogenesis of BOO differs from the pathogenesis of DO only in its greater degree of urethral obstruction, which leads to a decreased maximum flow rate, an increase in detrusor pressure at maximum flow, and an increased urethral resistance factor. It is accompanied by radiographic evidence of prostatic obstruction in men, and increased post-void residual urine in women.

Detrusor underactivity

Our assumption is that DU is the result of the stretching of the bladder by the large volume of urine during acute urinary retention. This condition can be compared with a balloon which deflates after having been inflated. As a result of losing its elasticity, the balloon does not return to its former state. In the rigid wall of the detrusor, the separated muscle cells are replaced by fibrous tissue, and the distance between weakened micromodules dramatically increases. The detrusor becomes so weakened that it cannot generate the pressure needed for the removal of quantities of urine below a certain threshold. At this volume the pressure in the bladder is equal to IAP. It begins to contract only after the inflow of an additional amount of urine, when the intravesical pressure rises from IAP to TP-1. After partial emptying, when the bladder pressure is lowered again to IAP, urination ceases and the same volume of urine is left in the bladder at low pressure. Our hypothesis is consistent with the hypothesis of Chancellor that the underactive bladder is a result of the progression of an overactive bladder[28].

CONCLUSION

The proposed hypothesis of motor function of the lower urinary tract in conjunction with the concept of age related rigidity of detrusor and urethral sphincters allows us to view the pathogenesis of various impairments of urination as a single process. This makes it possible to explain all the symptoms of LUTD. This hypothesis needs to be further tested.

DISCLOSURES

I am the only author of this theoretical work. I did not receive any support while working on it. The ideas of this work were not published before, and this article was not sent to other journals.

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Correspondence to:

Michael Levin
Amnon veTavar 1/2 - Netanya 42202 - Israel
E-mail: nivel70@hotmail.com