Comprehensive Treatment for Lower Urinary Tract Symptoms, Overactive Bladder and Bladder Outlet Obstruction in Men

Chieh-Lung Chou, M.D.
Department of Urology, China Medical University Hospital, Taichung, Taiwan

INTRODUCTION

Lower urinary tract symptoms (LUTS) are common in elderly men and have a negative impact on quality of life. Because the symptoms usually accompany benign prostate hyperplasia (BPH), the term "prostatism" was often used in the past, incorrectly referring to the prostate as the sole source of the typical LUTS found in aging men. With the understanding of the pathophysiology of male voiding disorders, we know that not only the prostate but also the urinary bladder is responsible for LUTS. Overactive bladder (OAB) is a condition characterized by symptoms of urinary frequency and urgency, with or without urge incontinence [1] which is often present in men with LUTS. The International Prostate Symptom Score (IPSS) includes obstructive and irritative symptoms. The irritative symptoms (frequency, urgency, nocturia) often can not be relieved by medical (α_1-adrenergic blockers and 5α-reductase inhibitors) or surgical (eg. trans-urethral resection of the prostate (TURP)) treatments targeting the prostate [2].

Consequently, the comprehensive treatment of LUTS, OAB and bladder outlet obstruction (BOO) should focus on the underlying factors causing the symptoms. In this article, we review issues related to the management of BOO/LUTS/OAB in men.

DIAGNOSIS OF BOO

BOO is a common cause of LUTS in men, but not all men with LUTS have BOO. Many studies have shown a lack of correlation of the IPSS 7 Index with urodynamic BOO. Although the IPSS is a valid clinical tool, it should not be used to judge the presence or severity of BOO [3]. The strategies for treatment of LUTS are different in men with BOO and those without BOO. Thus, it is very important to confirm the diagnosis of BOO in men with LUTS.

URODYNAMIC EVALUATION

By definition, BOO is determined by urodynamic studies assessing the pressure-flow relationship during voiding. Since the 1960's much study has been done to standardize the urodynamic definitions of obstruction in men. Today, pressure-flow studies remain the gold standard for the diagnosis of BOO and the etiology of LUTS [4].

WHO NEEDS URODYNAMIC EVALUATION?

Received: February 26, 2007 Accepted: March 6, 2007
Address correspondence to: Dr. Chieh-Lung Chou, Department of Urology, China Medical University Hospital, 91, Hsueh Shin Road, Taichung, Taiwan
E-mail: ericchou66@yahoo.com.tw

In the Agency for Health Care Policy and Research's (AHCPR) benign prostatic hyperplasia (BPH) guidelines, patients with a normal initial evaluation, and only mild symptomatology on the IPSS (scores 0 to 7), do not need additional diagnostic evaluation. Urinary flow rate, postvoid residual (PVR), and pressure-flow urodynamic studies are appropriate tests to evaluate men with moderate to severe symptoms (IPSS ≥ 8) [5]. Invasive diagnostic procedures are advised when patients have had a poor response to medical treatment and surgery is being considered. There is a significant chance the patient's LUTS may not be due to BPH according to clinical evaluation.

APPROPRIATE URODYNAMIC STUDIES

Uroflowmetry

This is a common, noninvasive urodynamic test used in the diagnostic evaluation of patients presenting with symptoms of BOO, and is usually their first urodynamic study. Uroflowmetry alone is insufficient to diagnose BOO because it cannot distinguish true obstruction from poor detrusor contractility [6]. The results of uroflowmetry are nonspecific for causes of the symptoms. For example, an abnormally low flow rate may be caused by an obstruction (e.g., hyperplastic prostate, urethral stricture, meatal stenosis) or by detrusor hypocontractility [7].

In the International Continence Society (ICS)-"BPH" study, Renard et al explored the relationship between uroflow variables and LUTS, and found that while uroflowmetry cannot replace pressure-flow studies in the diagnosis of BOO, it does have some diagnostic power when combined with symptoms [8]. Maximal flow rate (Qmax) has been reported to predict surgical outcome in patients undergoing prostatectomy for BPH. Jensen and associates [9] found that patients with a Qmax less than 15 mL/sec had a better subjective outcome after prostatectomy than those with a Qmax greater than 15 mL/sec. McLoughlin and coworkers [10] found that a Qmax of less than 12 mL/sec was a good indicator of obstruction.

Postvoid Residual Urine (PVR)

PVR urine is the volume of fluid remaining in the bladder immediately after the completion of micturition. This study is usually done after uroflowmetry.

Some clinical studies have demonstrated a minimal correlation between PVR and baseline measurements of symptoms, flow rate, and urodynamic measures of obstruction [11]. However, in the American Urological Association (AUA) outcome study, Barry and colleagues found a significant correlation between a high PVR and low flow rates but no correlation with the IPSS [12]. PVR is a "safety parameter." Men with significant PVRs should be monitored more closely if they elect nonsurgical therapy. However, the majority of men with elevated PVRs

are apparently not at high risk for complications [7].

Pressure-flow studies

If BOO can not be diagnosed after initial evaluation, (eg. uroflowmetry, PVR), further urodynamic assessment using pressure-flow studies should be considered, especially for patients in whom invasive treatment is being considered or who have had failed surgical treatment [13].

At present, the best method of analyzing voiding function quantitatively is the pressure-flow study of micturition, with simultaneous recording of abdominal, intravesical and detrusor pressures and flow rate [14]. Pressure-flow studies are most useful for distinguishing between urethral obstruction and impaired detrusor contractility. The test/re-test reliability of pressure-flow studies appears to be reasonable [15].

Nomograms have been developed to quantify pressure-flow plots in terms of one or more numerical parameters. Computerized analysis has facilitated the interpretation of pressure-flow data [16]. Commonly used nomograms include the Abrams-Griffiths nomogram, the Schafer method [17] (Fig. 1) and the ICS provisional nomogram [14] (Fig. 2).

Endoscopic examination

Cystoscopic evaluation of the lower urinary tract is most helpful in detecting anatomical or structural abnormalities (e.g., urethral strictures, bladder contracture, impacted urethral stones). However, it cannot be used to diagnose functional (sphincteric) or prostatic obstruction, and the appearance of the bladder wall (e.g., the presence of trabeculation) is not diagnostic [18]. Cystourethroscopy is suggested for men with LUTS who have a history of endoscopic urological surgery (eg. TURP) or urethra injury.

LUTS WITH BOO

The influence of BOO on bladder physiology and function

Partial BOO induces a series of morphological and functional changes in the bladder that have been previously reported to develop in 3 distinct phases [19-21]. Initially the bladder undergoes a remarkable growth period, referred to as the hypertrophy phase, which is accompanied by smooth muscle cell hypertrophy, and urothelial and fibroblast proliferation. After the growing bladder has reached a size that enables it to compensate for increased outlet resistance, it enters the compensation phase, which is associated with cessation of growth and maintenance of functional bladder capability. However, at some point the compensation phase can shift to the decompensation phase, during which the bladder experiences secondary growth accompanied by progressive deterioration in the ability to generate pressure and empty [20,21].

Changes in blood flow to the urinary bladder subsequent to partial BOO were observed in several basic studies. Shabsigh et al showed that partial BOO in rats rapidly stimulated bladder blood flow as early as 6 hours after partial BOO [22]. Schroder et al detected a clear correlation of bladder smooth muscle blood flow, bladder weight and the level of bladder decompensation 4 weeks after partial BOO. Decreased blood flow to the smooth muscle compartment paralleled the loss of contractile function in decompensated rabbit bladders with large weight gains [23].

Partial BOO is an established way to create bladder overactivity in animals. Neurotransmitter receptors may be upregulated or may exhibit increased sensitivity to the release of neurotransmitters after partial BOO. The onset of these changes may occur almost immediately after the detrusor is exposed to urethral obstruction. What is not known is when these changes become irreversible, even if the outlet obstruction is eventually relieved [24] Sutherland et al [25] investigated the histological changes in bladder innervation in response to partial BOO in a rat model. Cystometry showed functional alterations in bladder capacity and voiding pressures; obstructed animals had markedly increased bladder capacities and higher voiding pressures. They concluded that the neuropathic changes in the bladder after outlet obstruction, including detrusor instability, are mainly the result of anatomical perturbations in the cholinergic and adrenergic pathways [25].

TREATMENT OF LUTS WITH BOO IN MEN

Release of obstruction

Release of obstruction is crucial for the treatment of LUTS with BOO. De Nunzio et al analyzed the clinical and urodynamic long-term evolution of detrusor overactivity in a group of patients with BOO who were treated with watchful waiting, or medical or surgical therapy. They

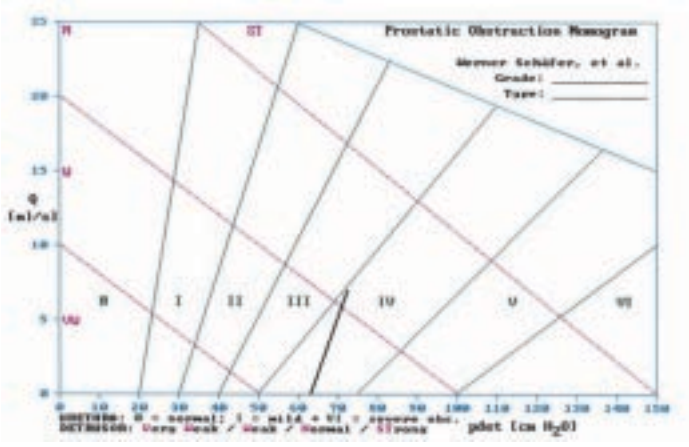

Fig. 1. Schafer nomogram. The plot shows that the patient falls into a grade III severity of obstruction with normal detrusor contractility. Pdet, detrusor pressure [18].

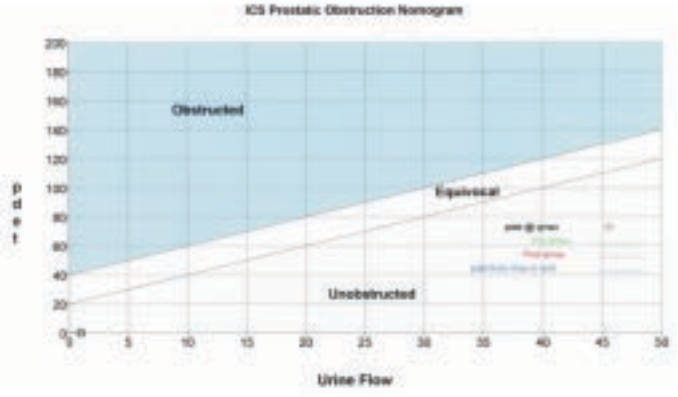

Fig. 2. Provisional International Continence Society nomogram. Patients are divided into three classes according to the bladder outlet obstruction index (BOOI) (PdetQmax - 2Qmax). BOOI > 40: obstructed; BOOI: 20 to 40: equivocal findings; BOOI < 20: unobstructed [18].

found detrusor overactivity is highly prevalent (52%) in patients with BOO, and appears to persist for long periods when obstruction is left untreated or treated only with medical therapy. However, surgical treatment of BOO, prostatectomy in particular, significantly reduces the incidence of detrusor overactivity and lessens the chance of its de novo appearance for up to 5 years [26].

Using intermittent catheterization can limit bladder distension during the initial phase of bladder response to outflow partial obstruction. Ohnishi et al using a rabbit model, showed that limiting distension with intermittent catheterization reduces the magnitude of the increased bladder mass, the loss of bladder wall elasticity (compliance), and the impaired contractile responses which occur secondary to outflow obstruction [27].

α-Adrenergic blockers

α-adrenergic blockers are the most commonly used medical treatment for BPH. BPH has 2 physiological components: a static component related to increased prostate size and a dynamic component related to increased prostate smooth muscle tone. α_1-adrenoceptors (AR) maintain prostate smooth muscle tone; hence, α_1-antagonists (blockers) relax prostate smooth muscle and decrease urethral resistance, ultimately leading to relief of LUTS [28]. Alpha-adrenergic blockers relieve not only obstructive but irritative symptoms in patients with BOO; mechanisms underlying the relief of irritative symptoms remain unknown. Chapple et al evaluated 135 patients with symptomatic urodynamically confirmed obstructive BPH treated for 12 weeks with either doxazosin (67 patients) or a placebo (68 patients) after an initial 2 week baseline evaluation. Twelve weeks' therapy with doxazosin resulted in significant improvement in hesitancy, impaired urinary stream, nocturia and urgency. Frequency improved with doxazosin therapy [29]. The study proved that α blockers are effective in relieving both obstruction and irritative symptoms.

The role of the sympathetic nervous system in detrusor function is still unresolved. Chou et al mapped the regional distribution of α_1 and β–adrenergic receptors (ARs) in rabbit ventral and dorsal bladder, and characterized the α_1-AR subtypes responsible for norepinephrine-induced contraction of rabbit dorsal detrusor smooth muscle. They found at least 4 heterogeneous regions with differing functional responses to adrenergic stimulation, that is (1) the dorsal and ventral dome, where β–ARs predominate, (2) the ventral detrusor, where β–ARs predominate, (3) the dorsal detrusor, where α_1-ARs predominate, and (4) the dorsal and ventral bladder neck, where α_1-ARs predominate. The authors mentioned a predominance of α_1-AR in human dorsal detrusor could be responsible for the irritative symptoms associated with benign prostatic hyperplasia. Studies are presently underway to determine if heterogeneity of detrusor responsiveness to sympathomimetics also occurs in the human bladder [30].

Subtypes of α_1 antagonists

α_1ARs mediate actions of norepinephrine and epinephrine through 3 α_1AR subtypes (α_{1a}, α_{1b} and α_{1d}) [31]. Non-subtype selective α_1AR antagonists relax prostate smooth muscle and relieve obstructive and irritative symptoms [32-35]. Prostate smooth muscle relaxation is mediated by α_{1a}ARs [36] and consequently subtype selective α_{1a}AR antagonists increase urine flow in benign prostatic hyperplasia [37]. However, α_{1a}AR antagonists do not appear to relieve irritative symptoms [37]. Gu et al investigated the effects of the α_{1a}AR antagonist 5-methyl urapidil (5 MU) vs the $\alpha_{1a/1d}$AR antagonist tamsulosin on urinary frequency in obstructed rats. The found that urinary frequency is increased in rats with a bladder mass greater than 500 mg. The combined $\alpha_{1a/1d}$AR antagonist tamsulosin decreased urinary frequency more than the α_{1a}AR selective antagonist 5 MU [38]. This finding supports the hypothesis that α_{1d}AR is important for mediating irritative symptoms.

5α-Reductase inhibitors

The design and chemistry of 5-α reductase inhibitors has been thoroughly studied and reviewed [39]. Two (finasteride and dutasteride) are now approved for human use. Finasteride was the first drug approved for use by the Food and Drug Administration (FDA) for treatment of BPH. Finasteride inhibits the type 2 isoenzyme of 5-α reductase, which is present in high levels in the prostate. A definitive multicentre trial was performed by the PLESS (Proscar Long-Term Efficacy and Safety Study) group and was reported in 1998 [40]. At the end of the study, patients treated with finasteride had a significantly greater decrease in AUA symptom score and a significantly greater increase in Qmax compared with those taking a placebo. Prostate volume also decreased by an average of 18% in the finasteride group compared with an increase of 14% in the placebo group.

Dutasteride, a type 1 and type 2 5-α reductase inhibitor, was approved for the treatment of BPH by the FDA in 2002. Dutasteride, because of its dual inhibition of 5-α reductase, reduces serum dihydrotestosterone levels by >90% [41]. The pooled results of these trials showed a significantly lower AUASS for the dutasteride arm versus the placebo, and a significantly higher Qmax for the dutasteride arm versus the placebo at 24 months. The prostate volume decreased by approximately 25% with dutasteride at 2 years [41,42]. Since 5α-reductase inhibitors reduce the prostate volume, it is reasonable that they ease irritative symptoms. The effect of 5α-reductase inhibitors on detrusor function is still to be determined.

Antimuscarnics

The incidence of OAB associated with BOO is 30%-60%.The symptoms of the two are similar and overlap. Detrusor instability has been modeled by partial BOO in several animal species. Schroder et al observed increased sensitivity to muscarinic receptor stimulation in the bladders of partial BOO rats, in which muscarinic receptor blockade caused a significant decrease in the contractile response in all groups [43]. In patients with benign prostatic hyperplasia, denervation has been found histologically and functionally in vitro [44,45]. It has been suggested that detrusor hypersensitivity to acetylcholine or increased electrical coupling in these areas causes uncoordinated contractions [46].

Antimuscarnics decrease the contractile response of the detrusor muscle of OAB patients. In a patient with BPH/LUTS with no evidence of BOO, particularly if the predominant symptoms are those of overactive bladder (OAB), treatment with an antimuscarinic agent is appropriate [29].

Combined α_1-adrenergic antagonist and antimuscarinic antagonist

Medical treatments that target the prostate (α_1-receptor antagonists and 5α-reductase inhibitors) often fail to alleviate OAB symptoms, and may not be the most appropriate therapy for men with storage LUTS [2]. Multiple studies have reported that antimuscarinic therapy

alone or in combination with α_1 -receptor antagonists improves OAB symptoms in men with and without BOO. Athanasopoulos et al published the result of combination treatment with an α_1 -blocker (0.4 mg tamsulosin orally once a day) plus an anticholinergic (2 mg tolterodine orally twice daily) for bladder outlet obstruction in 2003. They concluded that combination treatment with an α_1-blocker plus an anticholinergic improves the quality of life in patients with BOO and concomitant detrusor instability [47]. The proposed combination appears to be an effective and relatively safe treatment option in patients with bladder outlet obstruction and detrusor instability.

Similar results were reported in several studies. Lee et al evaluated the efficacy and safety of a therapeutic modality involving propiverine combined with doxazosin in patients with OAB and benign prostatic obstruction. A total of 211 men 50 years old or older with OAB symptoms and urodynamically proven BOO were randomized into 2 groups, and given either doxazosin (4 mg once daily) only or propiverine hydrochloride (20 mg once daily) plus doxazosin for 8 weeks. Patient satisfaction rates were found to be significantly higher in the combination therapy group than in the group taking doxazosin alone. This study reveals that combination therapy consisting of α_1-adrenoceptor antagonists with antimuscarinics represents an effective and relatively safe treatment modality in select patients with OAB coexisting with benign prostatic obstruction [48].

CONCLUSIONS

LUTS may be caused by aging, chronic bladder outlet obstruction, or changes in hormone status. In the evaluation of men with LUTS, in addition to prostate size, the presentation of voiding symptoms, uroflowmetry, and postvoid residual urine provide important information for the diagnosis of BOO. Further urodynamic studies, including pressure flow study or video-urodynamic studies, are suggested for patients who have a small prostate but also have severe irritative symptoms, especially before surgical intervention.

Studies have shown that α-adrenergic blockers relieve not only obstructive but also irritative symptoms in patients with bladder outlet obstruction. In a patient with BPH/LUTS with no evidence of BOO or with predominant symptoms of OAB, treatment with an antimuscarinic agent is appropriate. Combination treatment with an α_1-blocker plus antimusca-rinics appears to be an effective and relatively safe treatment option in select patients with OAB coexisting with benign prostatic obstruction. A thorough medical history, and high quality urodynamic studies help in selecting patients who can benefit from antimuscarinic therapy alone or in combination with alpha 1-receptor antagonists.

REFERENCES

1. Weber AM, Abrams P, Brubaker L, et al: The standardization of terminology for researchers in female pelvic floor disorders. Int Urogynecol J Pelvic Floor Dysfunct 2001; **12**:178-186.
2. Chapple CR, Roehrborn CG: A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: Focus on the bladder. Eur Urol 2006; **49**:651-659.
3. Sirls LT, Kirkemo AK, Jay J: Lack of correlation of the American Urological Association Symptom 7 Index with urodynamic bladder outlet obstruction. Neurourol Urodyn 1996; **15**:447-456.
4. Nitti VW: Pressure flow urodynamic studies: The gold standard for diagnosing bladder outlet obstruction. Rev Urol 2005; **7(Suppl 6)**: S14-21.
5. McConnell JD, Barry MJ, Bruskewitz RC, et al: Benign prostatic hyperplasia: Diagnosis and Treatment. Agency for Health Care Policy and Research. Clin Pract Guidel Quick Ref Guide Clin 1994; 1-17.
6. Chancellor MB, Blaivas JG, Kaplan SA, Axelrod S: Bladder outlet obstruction versus impaired detrusor contractility: The role of uroflow. J Urol 1991; **145**:810-812.
7. Lepor H, Lowe FC: Evaluation and Nonsurgical Management of Benign Prostatic Hyperplasia. In: Walsh PC, Retic AB, eds. Campbell's Urology, 8th ed, Philadelphia, Saunders, 2002, pp 1341.
8. Reynard JM, Yang Q, Donovan JL, et al: The ICS-BPH Study: Uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. Br J Urol 1998; **82**:619-623.
9. Jensen KM, Jorgensen JB, Mogensen P: Urodynamics in prostatism: I. Prognostic value of uroflowmetry. Scand J Urol Nephrol 1988; **22**:109-117.
10. McLoughlin J, Gill KP, Abel PD, Williams G: Symptoms versus flow rates versus urodynamics in the selection of patients for prostatectomy. Br J Urol 1990; **66**:303-305.
11. Griffiths HJL, Castro J: An evaluation of the importance of residual urine. Br J Radiol 1970; **43**:409-413.
12. Barry MJ, Cockett ATK, Holtgrewe HL, McConnell JD, Sihelnik SA, Winfield HN: Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. J Urol 1993; **150**:351-358.
13. Cockett ATK, Khoury S, Aso Y, et al: Proceedings of the 2nd International Consultation on BPH, Channel Islands, United Kingdom: Scientific Communication International, 1993.
14. Griffiths D, Hofner K, van Mastrigt R, Rollema HJ, Spangberg A, Gleason D: Standardisation of terminology of lower urinary tract function: Pressure-flow studies of voiding, urethral resistance and urethral obstruction. International Continence Society Subcommittee on Standardization of Terminology of Pressure-Flow Studies. Neurourol Urodyn 1997; **16**:1-18.
15. Rosier PF, de la Rosette JJ, Koldewijn EL, Debruyne FM, Wijkstra H: Variability of pressure-flow analysis parameters in repeated cystometry in patients with benign prostatic hyperplasia. J Urol 1995; **153**:1520-1525.
16. Van Mastrigt, van Mastrigt R: Urodynamic analysis using an on-line computer. Neurourol Urodyn 1987; **6**:206-207.
17. Schafer W: Analysis of bladder-outlet function with the line-arized passive urethral resistance relation, linPURR, and a disease-specific approach for grading obstruction: From complex to simple. World J Urol 1995; **13**:47-58.
18. Webster GD, Guralnick ML: The Neurourologic Evaluation. In: Walsh PC, Retic AB, eds. Campbell's Urology, 8th ed. Philadelphia, Saunders, 2002, pp 920-921.
19. Lindner P, Mattiasson A, Persson L, Uvelius B: Reversibility of detrusor hypertrophy and hyperplasia after removal of infravesical outflow obstruction in the rat. J Urol 1998; **140**: 642-646.
20. Levin RM., Haugaard N., Levin SS. et al: Bladder function in experimental outlet obstruction: pharmacologic responses to alterations in innervation, energetics, calcium mobilization, and genetics. In: Zderic S ed. Muscle, Matrix, and Bladder Function. Plenum Press: New York, 1995, pp 7.
21. Buttyan R, Chen MW, Levin RM: Animal models of bladder outlet obstruction and molecular insights into the basis for the development of bladder dysfunction. Eur Urol 1997; **32(Suppl 1)**:32-39.
22. Shabsigh A, Hayek OH, Weiner D, et al: Acute increase in blood flow to the rat bladder subsequent to partial bladder outlet obstruction. Neurourol Urodyn 2000; **19**:195-208.
23. Schroder A, Chichester P, Kogan BA, et al: Effect of chronic bladder outlet obstruction on the blood flow of the rabbit bladder. J Urol

2001; **165**:640-646.
24. Bauer SB: The effects and challenges of bladder outlet obstruction. J Urol 2000; **163**:3.
25. Sutherland RS, Baskin LS, Kogan BA, Cunha G: Neuroanatomical changes in the rat bladder after bladder outlet obstruction. Br J Urol Int 1998; **82**:895-890-901.
26. De Nunzio C, Franco G, Rocchegiani A, Iori F, Leonardo C, Laurenti C: The evolution of detrusor overactivity after watchful waiting, medical therapy and surgery in patients with bladder outlet obstruction. J Urol 2003; **169**:535-539.
27. Ohnishi N, Horan P, Levin S, Levin RM: Intermittent catheterization limits rabbit bladder dysfunction in response to partial outlet obstruction. J Urol 2000; **163**:292-295.
28. Schwinn DA, Price DT, Narayan P: Alpha-1-Adrenoceptor subtype selectivity and lower urinary tract symptoms Mayo Clin Proc 2004; **79**:1423-1434.
29. Chapple CR: Pharmacological therapy of benign prostatic hyperplasia/lower urinary tract symptoms: An overview for the practicing clinician. BJU Int 2004; **9**:738-744.
30. Chou EC, Capello SA, Levin RM, Longhurst PA: Excitatory alpha 1-adrenergic receptors predominate over inhibitory beta1-receptors in rabbit dorsal detrusor. J Urol 2003; **170**:2503-2507.
31. Michelotti GA, Price DT, Schwinn DA: Alpha-1 adrenergic receptor regulation: Basic science and clinical implications. Pharmacol Ther 2000; **88**:281-309.
32. Djavan B, Marberger M: A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. Eur Urol 1999; **36**:1-13.
33. Guthrie RM, Siegel RL: A multicenter, community-based study of doxazosin in the treatment of concomitant hypertension and symptomatic benign prostatic hyperplasia: The Hypertension and BPH Intervention Trial (HABIT). Clin Ther 1999; **21**:1732-1748.
34. Kumar VI, Dewan S: Alpha adrenergic blockers in the treatment of benign hyperplasia of the prostate. Int Urol Nephrol 2000; **32**:67.
35. Michel MC, Bressel HU, Mehlburger L, Goepel M: Tamsulosin: Real life clinical experience in 19,365 patients. Eur Urol 1998; **34(Suppl 2)**:37-45.
36. Forray C, Bard JA, Wetzel JM, et al: The alpha 1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned human alpha 1c subtype. Mol Pharmacol 1994; **45**:703-708.
37. Blue D, Zinner N, Grino P, Crager M, Ford A: RO700004, a selective α1A-adrenoceptor antagonist, does not improve lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol suppl 2002; **167**:265.
38. Gu B, Reiter JP, Schwinn DA, et al: Effects of alpha1-adrenergic receptor subtype selective antagonists on lower urinary tract function in rats with bladder outlet obstruction. J Urol 2004; **172**:758-762.
39. Li X, Chen C, Singh SM, Labrie F, Labire F: The enzyme and inhibitors of 4-ene-3-oxosteroid 5 alpha-oxidoreductase. Steroids 1995; **60**:430-441.
40. McConnell MD, Bruskewitz R, Walsh P, et al: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med 1998; **338**:557-563.
41. Roehrborn CG, Boyle P, Nickel JC, et al: Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002; **60**:434-441.
42. Sandhu JS, Vaughan ED Jr: Combination therapy for the pharmacological management of benign prostatic hyperplasia: Rationale and treatment options. Drugs Aging 2005; **22**:901-912.
43. Schroder A, Uvelius B, Newgreen D, Andersson KE: Bladder overactivity in mice after 1 week of outlet obstruction. Mainly afferent dysfunction? J Urol 2003; **170**:1017-1021.
44. Levin RM, Haugaard N, O'Connor L, et al: Obstructive response of human bladder to BPH vs. rabbit bladder response to partial outlet obstruction: A direct comparison. Neurourol Urodyn 2000; **19**:609-629.
45. Gosling JA, Gilpin SA, Dixon JS, Gilpin CJ: Decrease in the autonomic innervation of human detrusor muscle in outflow obstruction. J Urol 1986; **136**:501-504.
46. Mills IW, Greenland JE, McMurray G, et al: Studies of the pathophysiology of idiopathic detrusor instability: The physiological properties of the detrusor smooth muscle and its pattern of innervation. J Urol 2000; **163**:646-651.
47. Athanasopoulos A, Gyftopoulos K, Giannitsas K, Fisfis J, Perimenis P, Barbalias G: Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: A prospective, randomized, controlled study. J Urol 2003; **169**:2253 -2256.
48. Lee KS, Choo MS, Kim DY, et al: Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: A prospective, randomized, controlled multicenter study. J Urol 2005; **174**:1334-1338.