Sympathetic Hyperactivity in Lower Urinary Tract Dysfunction

En Meng, M.D., Ph.D.

Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

INTRODUCTION

As the population quickly ages, many countries must deal with problems resulting from continuing increases in the number of elderly people who need care. Elderly men have an increasing prevalence of benign prostatic hyperplasia (BPH) and concomitant lower urinary tract symptoms (LUTS), including frequency, incomplete voiding, nocturia, weak stream and sometimes difficulty in urinating. It has been reported that clinical BPH, which is characterized by moderate to severe LUTS, occurs in about one quarter of men in their 50s, one third of men in their 60s, and about half of all men 80 years old or older [1]. Erectile dysfunction (ED) has been reported by 28% of men from 40-65 years old and this adversely affects their quality of life [2,3]. In the 1990s, many researchers began to emphasize the number of elderly men with both LUTS and ED [4,5]. They suggested that sexual dysfunction is strongly associated with LUTS and this should be taken into account when managing patients with LUTS. There are currently four proposed pathophysiological mechanisms which support the relationship between LUTS and ED, reduced nitric oxide levels, the autonomic hyperactivity and metabolic syndrome, an alternative pathway for rhokinase activation/endothelin, and pelvic atherosclerosis [6]. Further understanding these mechanisms may help in developing new treatment strategies for both ED and LUTS.

Previous studies have demonstrated that LUTS secondary to BPH is a part of metabolic syndrome, which includes hypertension, obesity, dyslipidemia, glucose intolerance and insulin resistance, all known risk factors for ED [7,8]. Hammarsten, et al [8] analyzed 158 patients with LUTS secondary to BPH, and found men with the components of metabolic syndrome had significantly larger prostate volumes and higher annual BPH growth rates than those who did not. A second cohort of 258 patients with LUTS confirmed these results, supporting the hypothesis of a relationship between high insulin levels and the development of BPH, and giving rise to a hypothesis of increased sympathetic nerve activity in men with BPH [9]. The main effects of sympathetic innervation on the lower urinary tract are excitation of the bladder base and internal sphincter smooth muscle via α1-adrenergic receptors and inhibition of the parasympathetic pathway at the spinal and ganglion levels, therefore allowing the bladder to store urine. Increased sympathetic nerve activity in the bladder, prostate and urethra may elevate the tonicity of the bladder outlet and therefore cause lower urinary tract dysfunction.

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Address correspondence to: Dr. En Meng, Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, 325, Section 2, Chenggong Road, Neihu, Taipei, Taiwan
E-mail: mengen@ndmctsgh.edu.tw

EVIDENCE FROM BASIC RESEARCH

Autonomic hyperactivity, a component of metabolic syndrome, refers to a dysregulation of parasympathetic and sympathetic tone. Hypertension, obesity and hyperinsulinemia have all been claimed to be associated with increased sympathetic activity [7]. Mcvary and colleagues have demonstrated that unilateral sympathectomy leads to lesioned-side decreases in ventral prostate weight, DNA and protein content in rat models. This study suggests that alterations in autonomic activity can modulate prostatic growth and differentiation [10]. Spontaneously hypertensive rats (SHRs) have served as a rodent model for the spontaneous development of autonomic hyperactivity and BPH with age [11]. Increased tissue concentrations of norepinephrine and neuropeptide-Y immunoreactivity have been found in the urinary bladder, urethra and prostate of SHRs, indicating increased sympathetic innervation in these organs [12]. These animals void three times more frequently than controls. Urodynamic testing in SHRs demonstrated spontaneous bladder contractions at low volumes, an effect that was largely ameliorated by α-blockade [11]. This rat strain is also characterized by excessive neuroendocrine activity and their smooth muscle cells may produce increased amounts of nerve growth factor (NGF). NGF overproduction can contribute to hyperinnervation of different organs increasing further neurally mediated growth of the gland, or directly affect its growth [13]. It is suggested that upregulation of NGF production causes sensory and possibly noradrenergic pathways to elicit hyperactive voiding [14]. A recent study demonstrated that botulinum-A toxin injection into the prostate of rats alters cellular dynamics by inducing apoptosis, inhibiting proliferation and down-regulating α1A adrenergic receptors [15]. The rat model enables us to construct a link between LUTS and autonomic hyperactivity.

AUTONOMIC HYPERACTIVITY AND BENIGN PROSTATIC HYPERPLASIA/LOWER URINARY TRACT SYMPTOMS

An epidemiologic study has shown that men with increased sympathetic activity, including heart disease, β-blocker usage, and a sedentary lifestyle, were more likely to have symptomatic BPH [16]. Results from the Third National Health and Nutrition Examination Survey (NHANES III) and the Flint Men's Health studies have demonstrated a history of hypertension confers a 76% increased risk of LUTS [17]. It has also been reported that the annual BPH growth rate correlates positively with diastolic blood pressure [9].

A substudy of the Medical Therapy of Prostatic Symptoms (MTOPS) trial further reported that patients with BPH and a relatively small prostate (less than 20 cc) had symptoms that were managed adequately by α-blockade alone, suggesting that these symptoms were primarily related to sympathetic activity. They hypothesized that increased sympathetic activity may be related to the symptomatic de-

velopment and progression of BPH [18]. McVary et al, as part of the MTOPS study, evaluated autonomic nervous system activity in 38 men before enrolment. Tilt-table testing (a measure of autonomic tone and reactivity) revealed that increased sympathetic tone (as measured by changes in blood pressure, heart rate, urinary and serum catecholamine levels) was significantly associated with the level of LUTS even when controlling for cofactors known to influence sympathetic tone (age, body mass index, abdominal obesity, C-peptide and insulin levels, physical inactivity). Further analyses demonstrated that autonomic hyperactivity was strongly related to the total international prostate symptom score (IPSS), the BPH Impact Index and the bother score (IPSS question 8) and to a lesser extent to the prostate total volume and transitional zone volume. This study confirms that increased sympathetic tone (autonomic hyperactivity) can result in LUTS and subjective voiding complaints [19].

α-blockers have been used successfully to treat LUTS caused by BPH. α-blockers inhibit the adrenergic activation of α-adrenoceptors in the fibromuscular stroma and capsule of the prostate as well as in the central nervous system. However, whether the beneficial effects of α-blockers on LUTS are due to a direct effect of the drugs on the prostate or an indirect effect, e.g. in the central nervous system, is not clear. Many questions remain to be answered regarding the locations and roles of the α-adrenoceptors involved in modulating LUTS in men with BPH.

The final symptomatic experience of patients with LUTS secondary to BPH may be determined by two crucial factors. The first factor is the ability of the bladder to empty, including obstruction and poor muscular contractility. Pathological changes, including obstruction and poor muscular contractility, set the stage for the development of LUTS. The second factor may be an alteration in autonomic activity. Although there appears to be a significant link between autonomic hyperactivity and LUTS, it is unlikely that autonomic hyperactivity could be completely responsible for LUTS. Similarly, LUTS may not be attributable simply to an over perception of voiding difficulties by patients with BPH. Autonomic hyperactivity seems to have a key role in increasing the severity of LUTS above an intrinsic baseline intensity that is determined by the genitourinary anatomical characteristics of each patient with BPH. It is not currently clear whether the autonomic activity modulates the patient level of awareness of difficulty in voiding and/or whether it contributes directly to the physiological obstruction by sympathetic activation of the stromal smooth muscle in the prostate [19].

CONCLUSION

The current basic and clinical evidence has suggested that autonomic hyperactivity is strongly related to the urinary symptoms experienced by men with LUTS secondary to BPH. Modulation of the autonomic activity by α-blockade or other mechanisms allows for the alteration of symptoms without necessarily affecting the underlying defect or its progression. Further investigations into the quantitative measurement and relationship of autonomic activity to LUTS as well as anatomical alteration of the bladder outlet due to BPH may provide novel and important insights into voiding dysfunction in humans.

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