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Measures of autonomic nervous system activity and lower urinary tract symptoms

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Abstract

Autonomic nervous system (ANS) activity may play an important role in the development of lower urinary tract symptoms (LUTS). Men with severe LUTS and men with mild or no LUTS completed the Valsalva maneuver, quantitative sudomotor axon reflex test, tilt-table, and deep breathing tests. There were no differences between men with severe LUTS compared to men with mild or no LUTS (all P values > 0.05). Systemic ANS tests may not be useful in detecting the underlying physiologic changes that lead to LUTS in aging men.

Keywords

Autonomic nervous system; Lower urinary tract symptoms; Prostate enlargement

The development of lower urinary tract symptoms (LUTS) is a common problem in aging men. The α -1a adrenergic receptors (ARs) are responsible for prostate and bladder smooth muscle contractions, and α -AR inhibitors are commonly used for treating LUTS [1, 2]. In

addition, acetylcholine muscarinic receptors are present in the prostate and bladder, and antimuscarinic agents are effective for treating irritative LUTS [3, 4]. These data indicate that both the sympathetic and the parasympathetic components of the autonomic nervous system (ANS) have important roles in urologic function, and changes in these components may lead to the development of LUTS in aging men.

Studies examining associations between physiologic measures of the ANS and LUTS are limited, but a few studies suggest that ANS activity may be associated with LUTS [5, 6]. However, the tests used in these studies were not specific for α -adrenergic or muscarinic acetylcholine function, making it difficult to determine whether specific ANS components are important in the development of LUTS.

To address this issue, we studied a sample of men enrolled in a long-term cohort study of urologic conditions among men residing in Olmsted County, MN [7]. We identified 29 participants with severe LUTS [American Urological Association Symptom Index (AUASI) 18] on their most recent follow-up questionnaire (2006/2007), and an age-matched sample of 29 men (± 1 year) with none to mild LUTS (AUASI ≤ 7), and invited them to participate in a 1-h ANS screen at the Mayo Clinic Clinical Research Unit. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Participants refrained from food, coffee, and nicotine for 3 h prior to the study, and from using anticholinergic medications for 48 h. α - and β -antagonists were discontinued for 24 h with the permission of the patient's primary physician. Patients with severe diabetes or those who could not safely discontinue medications were excluded from participation. Compressive clothing was not worn the morning of the test, and participants avoided alcohol for 12–14 h prior to testing. Finally, all subjects emptied their bladders before testing.

Formal testing of changes in blood pressure during the four main phases of the Valsalva maneuver has been shown to provide a useful measure of adrenergic function [8, 9]. Participants were asked to maintain a column of mercury at 40 mmHg for 15 s by blowing into a bugle with an air leak, while blood pressure and heart rate were recorded continuously via a finger cuff [8]. Valsalva ratios (maximum heart rate divided by minimum heart rate) were calculated for each participant and blood pressure changes were measured during each phase to identify any abnormality.

The tilt-table test was used to provide a general measure of adrenergic function in study participants. Prior to undergoing the tilt-table test, participants rested for 30 min lying down. Twenty milliliters of blood was drawn into chilled catecholamine tubes containing ethylenediaminetetraacetic acid (EDTA)–sodium metabisulfite solution. Five minutes following a 70° tilt-up, blood samples were drawn again. Plasma was separated within 30 min of the blood draw and 7 mL of EDTA plasma was frozen immediately at -70°C . Catecholamines were adsorbed onto activated alumina at pH 8.6, washed and eluted with dilute acid. Norepinephrine, epinephrine and dopamine were separated using a reverse phase (C18) column, detected coulometrically and quantitated with the aid of an internal standard. Beat-to-beat blood pressure and heart rate were monitored throughout the study from an arm that remained at heart level throughout the tilt, for a 5-min period.

Quantitative sudomotor axon reflex test (QSART) results were used as a surrogate marker for cholinergic muscarinic activity in the prostate and bladder. Sweat output from four different sites (the forearm, proximal leg, distal leg, and foot) in response to acetylcholine iontophoresis was measured. A three-compartment capsule was used for this test; specifically, a 10% solution of acetylcholine was injected into one compartment and a constant current of 2 mA was applied for 5 min. After the acetylcholine was discontinued, sweat output was measured from a second compartment in the three-compartment capsule, with the area under the curve representing total sweat volume (measured in $\mu\text{L}/\text{cm}^2$) [9].

Participants were asked to breathe deeply at a rate of 6 breaths/min for 1 min. After 5 min of rest, subjects were asked to repeat this pattern for another minute. The five largest consecutive heart rate responses were read and averaged, and the heart rate range (maximum heart rate minus the minimum) was derived. There is currently no evidence to suggest that urologic function may be associated with vagal nerve function; these test results were used as a negative control for this study.

We compared distributional shifts in each measure between men with and without severe LUTS using Wilcoxon rank-sum tests. We also compared autonomic measurements between those with normal (prostate volume ≤ 30 mL) and enlarged prostate volumes (prostate volume > 30 mL). Analyses were conducted both including and excluding diabetic participants. As study results did not differ whether or not diabetics ($n = 6$) were included (data not shown), results are presented including all participants.

Overall, 37 (64%) men agreed to participate in this study; 19 had severe LUTS (AUASI ≥ 18) at their last visit, while 18 had none to mild LUTS (AUASI ≤ 7) at their last visit. Characteristics of participants are shown in Table 1. There were no significant differences in the results of the ANS screening tests in the men with severe LUTS compared to men with mild or no LUTS (Fig. 1) or in men with enlarged prostates compared to men without enlarged prostates (data not shown). Therefore, there was no evidence of a high sympathetic tone or excessive responses suggesting a hyperadrenergic state in men with severe LUTS.

These results differ from previous studies. McVary et al. [5] found associations between elevated urinary catecholamines, blood pressure readings, and heart rate measures following tilt-table testing and LUTS, prostate volume, and bother due to LUTS. Ullrich et al. [6] also found associations between increases in diastolic blood pressure and cortisol following a laboratory stress test and prostate enlargement and LUTS. More recently, Choi et al. [10] found that men with LUTS had lower measures of parasympathetic function compared to unaffected men. However, neither McVary nor Choi adjusted for multiple testing, making it possible that at least some of the observed associations were false-positives.

While our study results are negative, the results do not indicate that adrenergic and cholinergic functions are not important in male urologic health. Indeed, clinical trial results indicating the efficacy of α -AR inhibitors in treating LUTS and in delaying symptom progression argue for the importance of this system in urologic function [1, 2]. In addition, anticholinergics may be useful for treating the irritative symptoms that contribute to LUTS [11]. However, our results do suggest that the tests used in this study may not directly reflect

autonomic effects on the prostate or bladder. The autonomic tests in this study are most commonly used to detect autonomic failure and dysfunction, but some of the parameters analyzed may also indicate excess of function. These measurements, however, are not very sensitive due to the large variability and often skewed distribution of values even in normal populations, but can identify both hyper- and hypoadrenergic conditions [9, 12, 13].

The men who participated in this study had predominantly normal autonomic function, resulting in relatively little variation in their test results. We may have therefore lacked the power to detect small differences in autonomic function among men with varying levels of LUTS. However, our sample size was sufficient to detect relatively minor changes in continuous measures (including differences of 1.4 for the Valsalva ratio, 4.7–13.0 for the tilt-table test, and 1.0–1.4 for the QSART measures).

In summary, McVary's study [5] suggests that ANS overactivity (based on elevated responses to tilt-table testing) was associated with LUTS, while Choi's study [10] suggests that parasympathetic underactivity (based on lower high frequency heart rate measures) was associated with LUTS. Combined with our negative results, these data suggest that clearly defining the role of the ANS in the development of LUTS requires further study. Each of these studies was cross-sectional, making it impossible to sort out possible cause–effect relationships. It is possible that ANS changes that directly affect urologic function may occur early in life among men who will go on to develop LUTS, but later in life as a natural part of aging among men who do not develop LUTS. Longitudinal studies to assess whether changes in the ANS precede development of LUTS would eliminate problems that result from including men whose ANS problems develop after their LUTS in the study population. Therefore, prospective studies which measure ANS function prior to development of LUTS may be more useful for understanding the role of the ANS in the development of LUTS than cross-sectional studies among men with established LUTS.

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Fig. 1.

Differences in ANS test results between men with mild or no LUTS (*open circles*) and men with severe LUTS (*closed circles*). *P* values shown in the *upper right corner* of each plot compare the differences in ANS measures between these two groups using rank-sum tests

Table 1

Characteristics of the study population

Characteristics	Median (Q1, Q3)		Rank-sum <i>P</i> value
	Severe LUTS (<i>N</i> = 19)	Mild or no LUTS (<i>N</i> = 18)	
Age (years)	70.2 (62.8, 73.6)	70.1 (64.2, 77.3)	0.58
Height (cm)	180.5 (174.9, 183.4)	176.2 (173.3, 182.4)	0.27
Weight (kg)	97.3 (87.6, 101.8)	85.7 (74.2, 100.5)	0.12
BMI (kg/m ²)	28.4 (27.5, 32.6)	28.1 (24.5, 29.8)	0.37

BMI body mass index