Differences in Lower Urinary Tract Symptoms between Sympathetic Hyperactive and Hypoactive men

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A Dissertation Submitted to The Graduate School of
Ajou University in Partial Fulfillment of the Requirements for
The Degree of Ph. D. in Medicine

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June, 2015

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- ABSTRACT -

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Purpose

Heart rate variability (HRV) is a tool used to measure autonomic nervous function; however, there is no evidence that it can be used to define sympathetic hyperactivity in men with lower urinary tract symptoms (LUTS). I suspected that LUTS would differ between sympathetic hyperactive and hypoactive patients. Therefore, I measured HRV and divided the LUTS patients into two groups, a sympathetic hyperactive group and a sympathetic hypoactive group according to the low frequency/high frequency (LF/HF) ratio and made clinical comparisons between the groups.

Materials and methods

A total of 43 patients with symptomatic LUTS [International Prostate Symptom Score (IPSS) over 8] and 49 healthy volunteers were enrolled. No subjects had diseases that could affect the autonomic nervous system, such as diabetes or hypertension. Electrocardiographic signals were obtained from subjects in the resting state and HRV indexes were calculated with spectral analyses. I divided the LUTS patients into two groups by an LF/HF ratio of 1.9, which was the median value in the healthy volunteers, and compared the differences in clinical characteristics, IPSS, prostate-specific antigen (PSA),

and transrectal ultrasound (TRUS) results. The parameters were compared by independent sample t-test by use of SPSS version 19.

Results

There were no significant differences in age, serum PSA, or volume of the prostate between the 2 LUTS groups. The comparative results for parameters of HRV between the two groups showed only frequency on the IPSS questionnaire to differ significantly. ($p<0.05$)

Conclusion

I suggest that an imbalance of autonomic nervous system activity may be a factor and LUTS patients with hypoactive sympathetic tone may suffer from frequency and storage symptoms.

Key words: prostatic hyperplasia, autonomic nervous system, lower urinary tract symptoms, heart rate variability

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I. INTRODUCTION

Lower urinary tract symptoms (LUTS) are relatively common in aging men, and they have been known to greatly affect quality of life[1]. Because the number of men with benign prostatic hyperplasia (BPH) and LUTS continues to increase, it is important that the underlying pathogenesis of the disease is well understood. The relationship between LUTS and objective measures of BPH, such as prostate size and urodynamic parameters, has proved difficult to determine[2].

Heart rate variability (HRV) is widely used as a noninvasive tool that shows the balance of the cardiovascular system controlled by the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS)[3]. HRV is related to many urologic diseases, such as erectile dysfunction, female incontinence and chronic prostatitis[2, 4-6]. Recent studies have shown a correlation between ANS tone and LUTS, and with metabolic syndrome, which can affect ANS tone and also shows a correlation with BPH [7, 8]. However, not all patients with LUTS have sympathetic hyperactivity. Therefore, we investigated the clinical differences between LUTS patients with sympathetic hyperactivity and sympathetic hypoactivity.

II. MATERIALS AND METHODS

I selected 56 patients who visited an outpatient clinic for LUTS as patient group. No subjects had diseases that could affect the ANS, such as diabetes, hypertension, coronary heart disease, or any malignancy. No subjects had a history of surgery, irradiation or pelvic trauma. Among the 56 patients with LUTS, 43 patients who answered International Prostate Symptom Score (IPSS) questionnaire and IPSS 8 and over 8 points were finally included. The healthy volunteers as control group were selected who visited the family medicine outpatient clinic for a general health examination. To estimate the normal sympathetic tone and to divide the LUTS group into a sympathetic hypoactive and a sympathetic hyperactive tone group, I selected 49 healthy volunteers who were not statistically significantly different in clinical characteristics including age, IPSS, prostate-specific antigen (PSA), and trans-rectal ultrasound (TRUS) results. Then, I divided LUTS patients into two groups by low frequency/high frequency (LF/HF) ratio of 1.9, which was the median value in 49 healthy volunteers.

HRV Measurement

HRV was measured by using 2 methods: time domain and frequency domain analysis. The parameters of the time domain analysis were the mean heart rate in bpm, the standard deviation of the N-N interval (SDNN), and the square root of the mean squared difference of successive N-N intervals (RMSSD). SDNN reflects all of the cyclic components responsible for variability in the recording period and RMSSD represents parasympathetic activity. The parameters of the frequency domain analysis were total power (TP), very low frequency (VLF), LF, HFand LF/HF ratio. The HF peak of

the spectrum (0.15 to 0.40 Hz) represents parasympathetic activity, whereas the LF peak (0.04 to 0.15 Hz) represents sympathetic activity. Thus, the LF/HF ratio represents the ANS balance (sympathetic to parasympathetic).

I used a system developed in-house for HRV acquisition and signal processing to measure ANS activity. I confirmed that bladders were filled with more than 100 mL of urine before testing by ultrasonography to represent the physiological state. All subjects were restricted in their consumption of tea and coffee, cigarette smoking, and medication use (e.g., beta-receptor agonists or antagonists). After 30minutes of rest, each patient underwent electrocardiographic signal recording (SA-3000P, Medicore Co., Seoul, Korea) for 5 minutes while sitting. With the patients breathing normally, I calculated the mean heart rate, SDNN and RMSSD. I also determined the resting sympathetic and parasympathetic heartbeat rate modulation by using frequency domain methods, including TP, VLF, LF, HF, and LF/ HF ratio. HRV parameters were compared by using the independent sample t-test.

Statistical Analysis

Statistics were performed by using SPSS ver. 19.0 (SPSS Inc., Chicago, IL, USA). The data were presented as means ± standard deviations (SDs). Comparisons between the two groups were performed with the independent t-test P-values less than 0.05 were considered to be statistically significant.

III. RESULTS

Table1. Clinical characteristics between control and LUTS group.

	Control group (n=49)	LUTS group (n=43)	P-value
Age (yr)	61.4±10.4	58±7.8	0.40
Body mass index (kg/m2)	24.5±3.4	24.3±3.0	0.87
Total IPSS	4.69±1.55	17.3±6.9	0.01[1)]
PSA (ng/mL)	2.67±2.0	1.45±1.5	0.15
TRUS (mL)	31.41±9.1	32.7±13.8	0.82

Values are presented as mean ± standard deviation.
LUTS, lower urinary tract symptoms; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; TRUS, transrectal ultrasonopgraphy.
[1)]$P<0.05$

The t-test revealed that there were no significant differences between the control and LUTS groups in age, body mass index (BMI), serum PSA or volume of the prostate (Table 1). The mean age of LUTS group was 58 ± 7.8 years, PSA level was 1.45 ± 1.5 ng/ml, volume of the prostate by TRUS (trans-rectal ultrasonography) was 32.7 ± 13.8cc. By LH/HF ratio, LUTS group was divided into 2 groups as a sympathetic hypoactive and a sympathetic hyperactive group. Sympathetic hypoactive LUTS patients who LF/HF ratio below 1.9 were group 1, and sympathetic hyperactive LUTS patients who LF/HF ration over 1.9 were group 2. There was no significant difference in age, PSA, volume of prostate both LUTS groups. (Table 2.)

2. Table 2. The results of characteristics and IPSS parameters in two groups of LUTS patients by sympathetic activity

Variable	Group 1 (n=24)	Group 2 (n=19)	P-value
Age (yr)	59.6±9.3	58.8±7.8	0.25
PSA (ng/mL)	1.77±1.68	1.46±1.73	0.67
TRUS (mL)	29.4±9.1	32.2±12.0	0.21
IPSS parameters			
Q1	3.46±1.77	2.58±1.84	0.27
Q2	3.67±1.63	2.79±1.62	0.04[1)]
Q3	3.08±1.86	2.95±1.81	0.87
Q4	2.83±1.99	2.32±1.89	0.74
Q5	4.08±1.28	3.79±1.32	0.54
Q6	3.13±1.85	2.53±1.35	0.41
Q7	2.83±1.49	2.34±1.46	0.35
Total IPSS score	23.08±7.48	19.26±7.37	0.08
Quality of life	4.58±0.97	4.16±0.90	0.15
Voiding Sx score (Q1+Q3+Q5+Q6)/4	3.29±1.35	2.90±1.36	0.39
Storage Sx score (Q2+Q4+Q7)/3	3.02±1.44	2.11±1.26	0.03[1)]

Values are presented as mean±standard deviation.

Group 1, patients with LF/HF below 1.9; Group 2, patients with LF/HF 1.9 and over 1.9; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; TRUS, transrectal ultrasonography; Sx, symptom; Q, question number.

[1)]$P<0.05$

Analyzing parameters of IPSS questionnaire between two LUTS groups showed that there was significant difference in IPSS 2(frequent urination)(p=0.04) and average of storage symptoms in IPSS [(Q2+Q4+Q7)/3] (p=0.03). Sympathetic hypoactive patients suffered from storage symptom especially frequency than sympathetic hyperactive patients. The parameters about age, serum PSA, volume of the prostate were not significantly different.

IV. DISCUSSION

The extended underlying pathophysiology leading to LUTS remains unclear, although it is increasingly recognized that the causes of LUTS extend well beyond prostate enlargement and bladder outlet obstruction [9]. The multiple pathways leading to the onset and progression of LUTS not only complicate diagnosis, but also limit the overall effectiveness and satisfaction of targeted symptom management strategies [10]. The lower urinary tract is generally under the control of the ANS, is innervated by 3 sets of peripheral nerves (parasympathetic, sympathetic, and somatic nervous systems), and contains afferent and efferent motor axons [11].

HRV depends on the influence of sympathetic and vagal activity on the sinus node, and variability reflects spontaneous changes in autonomic activity [12]. HRV is a simple and important tool for studying the autonomic control of the heart and autonomic dysfunction, and it represents one of the most promising of such markers [13, 14]. As a development or progression, I suggest the possibility of ANS imbalance and use HRV as a method to evaluate ANS tone.

Previous epidemiological studies in men with BPH have suggested that a relationship between may exist between sympathetic overactivity and LUTS. Meigs et al noted that men with symptomatic BPH were also more likely to have characteristics known to be associated with increased sympathetic activation, specifically heart disease, β-blocker use, and a sedentary lifestyle [15]. Hammarsten and Hogstedt also found a relationship between more rapidly developing BPH and diseases including obesity, increased insulin, increased risk of type 2 diabetes and hypertension [16].

Choi et al reported ANS activity in men with voiding symptom-predominant

LUTS and storage symptom-predominant LUTS [17]. They showed that patients with LUTS exhibited decreased HF than healthy controls, which indicated that they may had some disease or imbalance in the ANS, that may distinguish LUTS patients from healthy men. However, the LF/HF ratio, which represents ANS balance, was not significantly different between LUTS patients and healthy controls. Thus, in the present study, I divided the LUTS patients into two groups by the median LF/HF value of the healthy controls. Because most investigators believe that LF and HF represent sympathetic and parasympathetic nervous system activity, respectively. Previous studies LUTS patients had an increased sympathetic tone, and voiding symptom predominant patients had more increased sympathetic tone. But our results suggest that LUTS patients could have relatively hypoactive sympathetic tone than healthy men, and they suffered from storage symptom more than those with hyperactive sympathetic tone, especially frequency.

Unfortunately, no specific modalities can be used to improve autonomic dysfunction. In some studies, HRV was improved by exercise or cessation of smoking. Accordingly, it may be beneficial for physicians to advise their patients to perform more exercise and to quit smoking [18, 19].

This study was limited in that LUTS are not specific and can be changed by factors unrelated to prostatic conditions, including diet, fluid intake, alcohol intake, anticholinergic effects of commonly used over-the-counter medications, smoking and even mood or physical activity [20-22]. I attempted to reduce such effects by asking patients to not consume anything that could affect the ANS before the HRV recording. Second, the sample size of both groups was small: thus, additional study with large numbers will be needed. Last, electrocardiography recording was measured only for 5 minutes in a sitting position and not for 24 hours to simplify the measurement and to

reduce the discomfort of the subjects.

Many patients suffer from LUTS that do not respond to current medications or surgical treatments, and I suggest that an imbalance in ANS activity may be a factor that cause or progression of diseases in men with LUTS. In particular, LUTS patients with hypoactive sympathetic tone may suffer from frequency and storage symptom by ANS dysfunction. I believe it is time to shift our concern to general health and ANS dysfunction to find the other etiologies of LUTS.

V. CONCLUSIONS

I suggest that an imbalance of autonomic nervous system activity may be a factor and LUTS patients with hypoactive sympathetic tone may suffer from frequency and storage symptoms.

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- 국문 요약 -

교감신경 활성도의 차이에 따른 하부요로 증상의 차이

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목적: 심박동수 변이 (heart rate variability)는 자율신경계 측정에 쓰이는 검사이나 하부요로증상 (lower urinary tract symptoms; LUTS)을 가지는 남성에서 교감신경 항진을 평가하는데 이를 사용할 수 있다는 증거는 없다. 우리는 교감신경의 활성도가 항진된 환자와 저하된 환자 사이에 하부요로증상이 다를 것이라 추정하였다. 그래서 나는 하부요로증상을 호소하는 환자의 심박동수 변이를 측정하여 low frequency/high frequency (LF/HF) ratio에 따라 교감신경의 활성도가 항진된 환자와 저하된 환자의 두 군으로 나누고 이들 사이의 임상적 차이점을 분석하였다.

재료 및 방법: 하부요로증상으로 내원한 환자 중 국제전립선증상점수 (International Prostate Symptom Score; IPSS)가 8 이상인 43명의 남성을 환자군으로, 건강한 성인남성 49명을 대조군으로 연구를 진행하였다. 연구에 참여한 환자군 및 대조군에서 당뇨나 고혈압 등 자율신경계에 영향을 미칠 수 있는 질환을 가지는 경우는 없었다. 심전도의 측정은 안정된 상태에서 시행하였고 심박동수 변이지표는 분광분석을 통해 계산되었다. 환자군은 대조군의 LH/FH ratio의 중간값인 1.9를 기준으로 두 군으로 나누었으며, 이 두 군 사이의 임상적 특징, 국제전립선증상점수, 전립선 특이 항원(prostate specific antigen; PSA) 및 경직장 전립선 초음파 (transrectal ultrasonography; TRUS) 등의 차이를 비교하였다. 통계 분석은 SPSS version 19 통계 프로그램을 이용하여 independent sample t-test를 시행하였다.

결과: 하부요로증상을 가진 두 군의 나이, 혈중 전립선특이항원 혹은 전립선의 크기에는 통계학적으로 유의한 차이는 없었다. 심박동수 변이를 나타내는 지표에 대한 비교분석에서는 국제전립선증상점수에서 오직 빈뇨 (frequency)에서만 통계적으로 유의한 차이를 나타내었다.

결론: 본 연구를 통해 자율신경계의 불균형이 하부요로증상을 야기하는 원인의 일부로 작용할 수 있다고 생각되며 특히 교감신경의 활성도가 저하된 환자에서 빈뇨 및 저장 증상이 심할 수 있다고 생각된다.

핵심되는 말: 전립선비대증, 자율신경계, 하부요로증상, 심박동수 변이