



# Changes in autonomic nervous system activity after treatment with alpha-blocker in men with lower urinary tract symptoms

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**Purpose:** To determine changes in autonomic nervous system activity after treatment in men with lower urinary tract symptoms (LUTS), we evaluated changes in patients' symptoms, uroflowmetry, and heart rate variability (HRV) after treatment with alpha-blockers for 12 weeks.

**Materials and Methods:** Ninety-five men who had LUTS (International Prostate Symptom Score [IPSS]  $\geq 8$ ) were included in this study. We divided them into two groups on the basis of a low frequency/high frequency (LF/HF) ratio of 1.6. After treatment with Xatral XL (Handok Inc., Korea) 10 mg for 3 months, we rechecked their IPSS, uroflowmetry, HRV and compared these with the baseline measurements.

**Results:** Fifty-four men were assigned to the low LF/HF group (group A: LF/HF  $\leq 1.6$ ) and 41 men to the high LF/HF group (group B: LF/HF  $> 1.6$ ). At baseline and 12 weeks, none of the parameters differed significantly between the groups except for HF, which is one of the parameters of HRV. IPSS, the IPSS-voiding subscore, and the IPSS-storage subscore decreased and maximal uroflow increased significantly after 12 weeks of treatment. Whereas the baseline LF/HF ratio increased from  $0.89 \pm 0.407$  to  $1.80 \pm 1.804$  after treatment in group A, it decreased from  $3.93 \pm 5.471$  to  $1.79 \pm 1.153$  in group B.

**Conclusions:** The efficacies of Xatral XL were clear in both groups. We found that the LF/HF ratio in the two groups merged to a value of approximately 1.79 after treatment. We suggest that this could be a clue to the importance of balance in autonomic nervous system activity in men with LUTS.

**Keywords:** Autonomic nervous system; Prostate; Urination

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## INTRODUCTION

Male lower urinary tract symptoms (LUTS) are diverse and complicated owing to their multifactorial etiology. LUTS can be a bothersome condition that leads to anxiety and even morbidity, and treatment outcomes vary for similar reasons [1].

It is well known that the autonomic nervous system (ANS) regulates the micturition cycle, and central sympathetic overactivity can be associated with idiopathic overactive bladder [2]. Our previous studies showed a marked relationship between an imbalance in ANS activity and LUTS in men [3-5]. Therefore, we can infer that ANS activity may change after improvements in LUTS with alpha-blocker treatment or that the efficacy of treatment may differ according to ANS activity.

In this study, we used an alpha-blocker to treat male LUTS because many clinical trials have established alpha-blockers as a basic medicine for improving LUTS [6]. Alpha-blockers relieve bladder outlet resistance by smooth muscle relaxation of the prostate and bladder neck [6,7] and are a fast, effective treatment option [8].

Many tests are available for evaluating autonomic activity, such as the Valsalva ratio, thermoregulatory seat test, and the tilt table [9]. We used heart rate variability (HRV) to compare the subjects' ANS activity before and after treatment with an alpha-blocker because of its quantitative, noninvasive characteristics. HRV is a simple, reproducible test that is easy to implement in a clinical situation.

The objectives of this study were to determine changes in ANS activity after treatment with an alpha-blocker for 12 weeks and to compare differences in treatment efficacy according to the low frequency (LF)/high frequency (HF) ratio, which is a measure of the ratio of sympathetic to parasympathetic activity.

## MATERIALS AND METHODS

This was a subgroup analysis of a prospective, multicenter, open-label observational study reported in 2015 [5]. Between June 2011 and February 2013, 169 men were screened in 11 hospitals in Korea. The study protocol was reviewed by the Aju University Institutional Review Board and approved (approval number: MED-SUR-10-338). Informed consent was obtained from all individual participants included in the study. The inclusion criteria were men aged  $\geq 50$  years with a total International Prostate Symptom Score (IPSS)  $\geq 8$ , maximal uroflow (Q<sub>max</sub>) rate  $\leq 15$  mL/s, and

a period of more than 3 months with LUTS. The exclusion criteria were allergic drug reaction to alpha-blockers, orthostatic hypotension, renal or hepatic impairment, neurogenic bladder, a history of surgery for the prostate or a pelvic organ, a serum prostate-specific antigen (PSA) value  $\geq 10$  ng/mL, and history of taking any alpha-blocker for more than 4 weeks or 5-alpha-reductase inhibitors for more than 6 months before baseline. We informed the patients with a PSA level over 4 ng/mL of the need to have their PSA levels rechecked or to undergo biopsy. Subjects who were receiving or were planning to be treated with the following drugs that could affect ANS activity were excluded: alpha- or beta-receptor agonists or antagonists, antihypertensive drugs, antipsychotics, anticholinergics, anxiolytics, or antidepressants. Men with accompanying disease that could influence ANS activity were also excluded, such as diabetes, hypertension, neurologic disease, cardiovascular disease, or any malignancies.

IPSS and uroflowmetry were assessed at baseline. We also measured the subjects' HRV at baseline by using an in-house system. The subjects were then divided into two groups according to their LF/HF ratio, which is one of the HRV parameters. Men with LF/HF  $\leq 1.6$  were classified into group A, and the others were placed in group B. We used 1.6 as the cutoff because we had calculated the mean value of LF/HF in 118 healthy volunteers in a previous study. All subjects were treated with Xatral XL (Handok Inc., Seoul, Korea) 10 mg once daily for 12 weeks, after which we evaluated HRV, IPSS, and uroflowmetry again. We analyzed changes in total IPSS, IPSS-voiding subscore (sum of IPSS no. 1, 3, and 5), IPSS-storage subscore (sum of IPSS no. 2, 4, 6, and 7), Q<sub>max</sub>, and LF/HF ratio after 12 weeks of treatment.

The primary endpoint of this study was the difference in change in the LF/HF ratio after treatment with Xatral XL 10 mg for 12 weeks compared to baseline. Secondary endpoints were the change in IPSS and Q<sub>max</sub> after treatment.

### 1. HRV measurement

We used HRV as measured with the SA-3000p (Medicore, Seoul, Korea) to evaluate the subjects' ANS activity at baseline and after 12 weeks. Before HRV measurement, all subjects received a bladder scan to confirm that their bladder contained at least 100 mL of urine. We prohibited consumption of tea or coffee and food and cigarette smoking to avoid any influence on ANS activity. We took each subject's electrocardiographic signal recording for 5 minutes while he was sitting in a comfortable position, and then measured LF (0.04 to 0.15 Hz) and HF (0.15 to 0.40 Hz) by

frequency domain analysis to calculate the LF/HF ratio.

**2. Statistical analysis**

We used IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA) to analyze the differences in parameters with the paired t-test in each group. To evaluate differences in parameters between groups, we used independent t-tests. A p-value of <0.05 was considered statistically significant. All data in this study were expressed as mean±standard deviation.

**RESULTS**

A total of 169 men were screened, and 95 men who finished the study protocol were included in the study (Fig. 1) and assigned to group A (LF/HF ≤1.6, n=54) or group B

(LF/HF >1.6, n=41). Baseline characteristics did not differ significantly between the groups, except for HF, which was higher in group A (Table 1). Treatment with Xatral XL 10 mg induced statistically significant improvement in LUTS in both groups (Table 2). Total IPSS in both groups decreased after treatment compared with baseline; however, we could not detect any difference in treatment efficacy between groups. The IPSS-voiding subscore and IPSS-storage subscore decreased in the same manner as the total IPSS, and we could not find any significant differences between the groups. Qmax increased significantly after treatment with Xatral XL 10 mg for 12 weeks in both groups; however, there was no significant difference between groups.

In group A, the LF/HF ratio at baseline was 0.89±0.407 and it increased to 1.80±1.804 after 12 weeks with Xatral XL 10 mg. By contrast, the LF/HF ratio decreased from 3.93±5.471

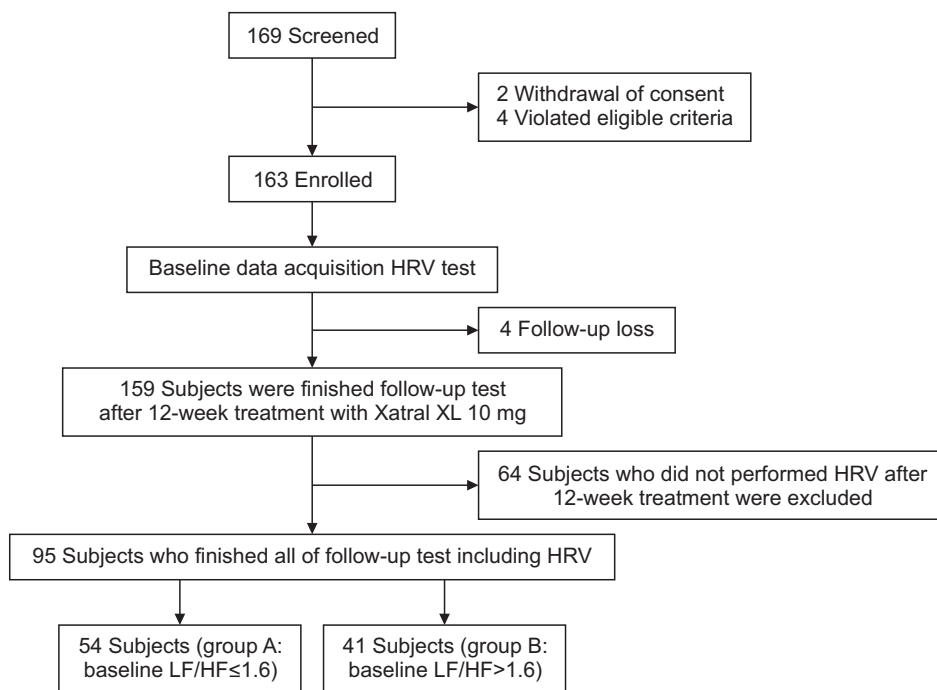


Fig. 1. Patient disposition and enrollment. HRV, heart rate variability; LF, low frequency; HF, high frequency.

Table 1. Characteristics of the subjects at baseline

Characteristic	Group A (n=54)	Group B (n=41)	p-value
Age (y)	65.5±7.68	62.7±5.75	0.055
LF (ms <sup>2</sup> )	104.5±128.22	132.9±105.95	0.253
HF (ms <sup>2</sup> )	137.7±216.28	47.8±43.64	0.010
LF/HF	0.89±0.407	3.93±5.471	0.001
Total IPSS	15.8±5.68	15.7±5.60	0.936
IPSS-voiding subscore	9.9±4.89	9.4±3.82	0.622
IPSS-storage subscore	5.9±2.90	6.2±3.00	0.582
Qmax (mL/s)	10.3±4.17	9.4±4.00	0.297

Values are presented as mean±standard deviation.

Group A, LF/HF ≤1.6; group B, LF/HF >1.6; LF, low frequency; HF, high frequency; IPSS, International Prostate Symptom Score; Qmax, maximal uroflow.

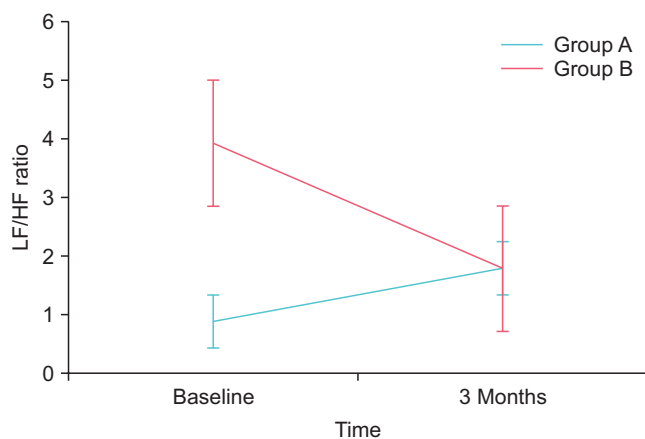
**Table 2.** Change in mean total IPSS, IPSS subscores, Qmax, and LF/HF ratio after treatment with Xatral XL 10 mg for 12 weeks

Parameter	Group A		Group B	
	Baseline	12 weeks	Baseline	12 weeks
Total IPSS	15.7±5.62	10.9±6.13 <sup>a</sup>	15.8±5.68	10.1±6.11 <sup>a</sup>
IPSS-voiding subscore	9.7±4.20	6.4±4.11 <sup>a</sup>	9.9±4.49	6.0±4.35 <sup>a</sup>
IPSS-storage subscore	6.1±2.93	4.6±2.75 <sup>a</sup>	5.9±2.90	4.1±2.56 <sup>a</sup>
Qmax (mL/s)	10.3±4.17	15.7±8.00 <sup>a</sup>	9.31±3.99	14.0±7.94 <sup>a</sup>
LF (ms <sup>2</sup> )	104.5±128.22	197.4±452.48 <sup>a</sup>	132.9±105.95	209.0±343.34 <sup>a</sup>
HF (ms <sup>2</sup> )	137.7±216.28	138.98±175.81	47.8±43.64	161.6±175.81 <sup>a</sup>
LF/HF <sup>b</sup>	0.89±0.407	1.80±1.804 <sup>a</sup>	3.93±5.471	1.79±1.153 <sup>a</sup>

Values are presented as mean±standard deviation.

IPSS, International Prostate Symptom Score; Qmax, maximal uroflow; LF, low frequency; HF, high frequency; group A, LF/HF ≤1.6; group B, LF/HF >1.6.

<sup>a</sup>:Difference from baseline, p<0.05. <sup>b</sup>:Difference between groups, p<0.05.



**Fig. 2.** Change in low frequency (LF)/high frequency (HF) ratio after treatment with Xatral XL (group A: LF/HF ≤1.6, group B: LF/HF >1.6).

to 1.79±1.153 in group B (p=0.01, Fig. 2).

## DISCUSSION

The lower urinary tract is controlled by the ANS, which includes sympathetic and parasympathetic activity. The storage or voiding function of the bladder is the result of a complex series of processes by the lower urinary tract governed by ANS activity. The activation of sympathetic nerves inhibits bladder activity and stimulates the internal urethral sphincter [10]. The prostate is also innervated by the sympathetic and parasympathetic nervous system [11]. Prostate growth is associated with ANS activity. McVary et al. [12] showed in a study with aging rats that increased autonomic activity results in prostatic hyperplasia, and removal of the innervation induces regression of prostate weight. In another study, those authors suggested that ANS hyperactivity is related to LUTS severity and prostate size [13]. Thus, we can easily guess that an imbalance in ANS activity between sympathetic and parasympathetic activity

could affect lower urinary tract function to induce LUTS.

HRV can affect the influence of sympathetic and vagal activity on the sinus node, and variability reflects spontaneous changes in ANS activity. HRV is a simple and reproducible index for evaluating autonomic control of the heart and autonomic dysfunction [14]. The clinical importance of HRV became apparent in the 1980s when HRV was identified as a strong predictor of mortality from acute myocardial infarction [15]. Most investigators believe that the root mean square successive difference and HF are predominantly a response to changes in parasympathetic tone, whereas standard deviation of the mean of qualified NN-interval and LF are influenced by adrenergic and cholinergic activities [16]. In clinical and experimental observations of autonomic tests, efferent vagal activity can be a major contributor to HF [17], and the LF component is considered to be a marker of sympathetic modulation by investigators [18]. Finally, LF and HF in HRV refer to sympathetic and parasympathetic activity, respectively, so we can say that the LF/HF ratio refers to the balance of ANS activity. Thus, the LF/HF ratio is considered to be a marker that mirrors the balance of sympathetic and parasympathetic activity, reflecting sympathetic modulation [19]. A high LF/HF ratio indicates that sympathetic nerve activity is higher than parasympathetic nerve activity. Although it is a good marker for ANS activity, cutoff values for identifying sympathetic hyperactivity have not been identified.

HRV has several limitations for acquiring precise values for each parameter because too many factors affect the human body. For example, if the patient took medication that can affect the ANS before the HRV test, the test results could be an error. In the present study, we excluded subjects with diseases that can affect the ANS and attempted to restrict subjects from ingesting food, tea,

or coffee; cigarette smoking; and medications before HRV recording. We tried to perform the measurement of HRV in a clinical manner, with confirmed bladder filling to at least 100 mL before testing and with the subjects lying down to rest for 10 minutes with normal breathing before the test.

In a pilot study of HRV in men with LUTS, the patients with LUTS had lower HF than did men in the healthy control group, and men with predominant voiding symptoms had a higher LF/HF ratio than did men with predominant storage symptoms [4]. These findings indicated that an imbalance in ANS activity could be related to the cause or mechanism of the appearance of LUTS.

Because we found no normal values for identifying ANS activity with HRV parameters in Korean men, we performed a pilot study with healthy volunteers to identify the standard LF/HF ratio. We evaluated HRV in 118 healthy volunteers from a health promotion center to get values of LF/HF in men without LUTS. The men were aged between 40 and 70 years and had a total IPSS of less than 8. HRV was evaluated in the same manner as in the study protocol to get a mean of LF/HF ratio, which was found to be 1.6. We therefore defined an LF/HF of less than or equal to 1.6 as sympathetic hypoactivity and an LF/HF of greater than 1.6 as hyperactivity. We divided the subjects according to their LF/HF ratio to compare treatment efficacies and change in LF/HF after treatment with Xatral XL 10 mg for 12 weeks.

Xatral XL is a nonselective, slow-release alpha-blocker and a representative medication with acceptable safety profiles for male LUTS patients [20,21]. Xatral XL was significantly effective for improving the patients' symptoms and increasing Qmax in men with both a high LF/HF ratio and a low LF/HF ratio. Between the two groups, changes in total IPSS, IPSS-voiding subscore, and IPSS-storage subscore after treatment were not significantly different.

The most interesting finding was the change in the LF/HF ratio in each group. The LF/HF ratio was increased after treatment in group A, whereas it decreased in group B (Fig. 2). After 12 weeks of treatment with Xatral XL the LF/HF ratio in the two groups merged at approximately 1.79. This suggests that balancing ANS activity may be important for improving LUTS. In other words, an imbalance in ANS activity could be a cause or mechanism in the development of LUTS.

As in previous studies, the results of our study suggest that ANS dysfunction, especially an imbalance between sympathetic and parasympathetic activity, could be implied in idiopathic overactive bladder and that a balanced ANS is very important for maintaining lower urinary tract function.

## CONCLUSIONS

It is widely known that LF reflects sympathetic activity and HF reflects parasympathetic activity. We can use HRV to evaluate a patient's autonomic function, and the LF/HF ratio can be considered to be a measure of the balance of the ANS. In this study, the mean LF/HF ratio in subjects who had a high LF/HF ratio at baseline was decreased after treatment and that in men with a low LF/HF at baseline was increased. That is, the LF/HF ratios in each group merged to approximately 1.79, near the value in healthy people. This study has shown how ANS balance is important for improving LUTS and is related to treatment efficacy with alpha-blockers. This finding is a clue that an imbalance in the ANS may be a causative factor for LUTS and may influence the efficacy of treatment.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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