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Alteration of Autonomic Function in Female Urinary Incontinence

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Purpose: Stress urinary incontinence (SUI) and urge urinary incontinence (UUI) have different mechanisms of action. We believe that alteration of autonomic nervous system (ANS) activity may contribute to UUI because the lower urinary tract is regulated through the sympathetic and parasympathetic nervous systems. Heart rate variability (HRV) allows measurement of autonomic nervous function, therefore we measured and compared HRV parameters in women with urinary incontinence.
Methods: From March 2008 to March 2010, we evaluated all patients who visited 2 university hospitals for treatment of urinary incontinence. Theywere performed 3-day voiding diary, urodynamic study, physical examination and routine laboratory examination. We excluded subjects who had diabetes, cardiovascular problems, or other condition that affect ANS. Patients with mixed urinary incontinence (MUI) were also excluded. Finally 47 women with SUI (group 1) and 29 women with UUI (group 2) were enrolled according to their symptoms and voiding diary. We compared their HRV parameters. And excluding 11 patients who had detrusor underactivity, we divided them again into group A, 53 women without detrusor overactivity (DO) and group B, 12 women with DO. We compared HRV parameters between DO and non-DO group.
Results: Older women had a higher incidence of UUI and DO. In HRV parameters, only the ratio of low frequency (LF) and high frequency (HF) was significantly higher in group 2 than group 1 (3.5 ± 3.6 vs. 1.6 ± 1.1, $P < 0.05$). Also group A had higher mean LF/HF ratio than group B (4.3 ± 3.8 vs. 1.9 ± 1.9, $P < 0.05$).
Conclusions: Increased LF/HF values indicate relative sympathetic hyperactivity over parasympathetic activity. Changes in ANS activity could indicate the presence of UUI and potentially DO.

Keywords: Heart rate; Incontinence; Autonomic nervous system

INTRODUCTION

Urinary incontinence is the complaint of any involuntary urine leakage proven objectively and a problematic issue socially and hygienically in women [1]. Although urinary incontinence rarely causes mortality, its social budget and impact on individual life is enormous. We classify the type of urinary incontinence with their symptoms and mechanisms to induce urine leakage. Stress incontinence means involuntary urine leakage on abdominal straining, exertion, sneezing or cough, and it has a higher incidence and prevalence than urge incontinence. The pathophysiology of stress urinary incontinence (SUI) is moderately well understood, but the etiology and mechanism of urge urinary incontinence (UUI) are still unclear. It is assumed that urge urinary incontinence with overactive bladder (OAB) could be the result of abnormality at bladder or neurologic abnormality but the mechanism and pathogenesis are not clearly understood [2]. The pathophysiology of idiopathic OAB is also unclear, but two hypotheses dominate as myogenic and neurogenic dysfunction [3-5].

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Structurally bladder and urethra are composed of smooth muscle and connective tissue mainly [6]. There are 3 types of nervous system innervating lower urinary tract; parasympathetic, sympathetic and somatic nervous system [6-8]. Autonomic nervous system (ANS) plays an important role in regulating bladder function, therefore if there is any change in ANS, bladder function will be influenced.

Autonomic dysfunction may disrupt bladder function and sphincter activity [9,10] because the lower urinary tract is innervated by the autonomic and somatic nervous system, however autonomic dysfunction in urinary disorders is difficult to measure [11]. Several studies revealed autonomic dysfunction could contribute to the pathogenesis of urgency and nocturnal enuresis in children [9,10,12,13]. Recently Im et al. [14] reported autonomic dysfunction may cause lower urinary tract symptom via disrupted control of the sympathetic and parasympathetic nervous systems.

Heart rate variability (HRV) can be used to assess sympathetic and parasympathetic activity, is widely used in cardiologic research field [15,16], and provides qualitative, quantitative, and noninvasive analysis of global autonomic function. The test is based on physiologic principle that the HRV is reflecting the sympathovagal tone and it can be quantified as the frequency of the sino-atrial node of the heart. We compared the parameters of HRV to identify alteration of ANS in patients showing symptoms of urinary incontinence.

MATERIALS AND METHODS

Patients Characteristics

From March 2008 to March 2010, all female patients who visiting hospital for treatment of urinary incontinence were performed a history taking, physical examination, urinalysis, voiding diary, King's health questionnaire and urodynamic study. The study inclusion criteria included being a woman, having urinary incontinence, at least once a day on voiding diary, and an age greater than 18 years old. Excluding criteria were the presence of any urinary tract infection, malignancy, pregnancy, severe grade urogenital prolapsed (grades III and IV), and any disease which can affect autonomic nervous system function, such as diabetes, hypertension and so on. SUI was defined as urinary incontinence on physical exercise based on their symptoms. UUI was defined as urinary incontinence with urgency, at least once a day on voiding diary. All patients who have both of SUI and UUI were excluded. Finally 76 women with urinary incontinence were enrolled, they were divided into two groups based on voiding diary and symptoms as group 1 (patients with pure SUI, 47 patients) and group 2 (patients with UUI, 29 patients). All patients were evaluated with urodynamic study. We defined detrusor overactivity (DO) as involuntary increasing detrusor pressure over 25 cmH_2O and urodynamic incontinence with involuntary increasing detrusor pressure even below 25 cmH_2O in filling cystometry. On the other hand, 65 patients except who had acontractile detrusor in voiding cystometry or pressure flow study (11 patients) were divided again into two groups: group A, patients without DO (53 patients) and group B, patients with DO (12 patients).

HRV Test

HRV test was performed using 2 methods: time domain and frequency domain analysis. Parameters of time domain analysis were the mean heart rate in bpm, standard deviation of the N-N interval (SDNN), and the square root of the mean squared differences 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. Parameters of frequency domain analysis were total power (TP), very low frequency (VLF), low frequency (LF), high frequency (HF), and LF/HF ratio. The HF peak of the spectrum (0.15 to 0.40 Hz) represents parasympathetic activity, while the LF peak (0.04 to 0.15 Hz) represents sympathetic activity. Thus, the LF/HF ratio represents the ANS balance (sympathetic to parasympathetic).

We used a system developed in-house for HRV acquisition and signal processing to measure ANS activity. We 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 30 minutes of rest, each patient underwent electrocardiographic signal recording (SA-3000P, Medicore Co., Seoul, Korea) for 5 minutes while sitting. With the patients breathing normally, we calculated the mean heart rate, SDNN and RMSSD. We also determined the resting sympathetic and parasympathetic heartbeat rate modulation using frequency domain methods, including TP, VLF, LF, HF, and LF/HF ratio. HRV parameters were compared using the independent sample t-test, and other differences between group 1 and 2, group A and B were analyzed by Mann Whitney U test. Statistical calculations were performed using SPSS ver. 12.0 (SPSS Inc.,

Chicago, IL, USA). A P-value was considered significant if $P < 0.05$.

RESULTS

The Difference of HRV Parameters between Group 1 and Group 2

The mean age of patients in group 1 was 46.4 ± 13.1 years old, and that of group 2 was 53.8 ± 13.4 years old (P = 0.030).

On time domain analysis, the mean SDNN and RMSSD of the patients in two groups were not significantly different. On frequency domain analysis, the mean values of TP, VLF, LF, and HF in two groups were not significantly different. However, the mean value of the LF/HF ratio in group 2 was significantly higher than group 1 (3.5 ± 3.6 vs. 1.6 ± 1.1, P = 0.003) (Table 1).

The Difference of HRV Parameters between Group A and Group B

The mean age of group A was 47.4 ± 13.5 years old and that of group B was 57.3 ± 11.0 years old (P = 0.021). All laboratory results were within the reference range.

The mean SDNN and RMSSD of the patients in two groups were not significantly different. The mean values of TP, VLF, LF, and HF in the two groups were not significantly different, but, the mean LF/HF ratio in group B was higher than group A (4.3 ± 3.8 vs. 1.9 ± 1.9, P = 0.003) (Table 2).

Table 1. Parameters of heart rate variability for group 1 and group 2

	Group 1 - SUI (n = 47)	Group 2 - UUI (n = 29)	P-value
SDNN (ms)	34.2 ± 19.1	30.2 ± 19.7	0.426
RMSSD (ms)	26.4 ± 22.4	19.0 ± 10.6	0.127
HR (bpm)	74.7 ± 9.0	83.8 ± 40.3	0.180
TP (ms^2)	952.3 ± 1,194.8	618.5 ± 670.7	0.207
VLF (ms^2)	497.4 ± 536.7	412.9 ± 626.8	0.565
LF (ms^2)	236.4 ± 375.3	114.2 ± 105.1	0.118
HF (ms^2)	218.4 ± 451.8	91.5 ± 122.2	0.175
LF/HF ratio [a]	1.6 ± 1.1	3.5 ± 3.6	0.003

Values are presented as mean ± SE.
SUI, stress urinary incontinence; UUI, urge urinary incontinence; SDNN, standard deviation of the N-N interval; RMSSD, square root of the mean squared differences of successive N-N intervals; HR, heart rate; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency.
[a] P < 0.05 by Mann-Whiney U test.

DISCUSSION

Urinary incontinence and OAB are common disorders in women, but perhaps only 15% of patients with urinary incontinence and OAB have sought medical help [17]. Although not life-threatening, incontinence is bothersome and deteriorates quality of life because it can occur with the bladder full or empty during work or sleep [18]. The overall prevalence of incontinence ranges from 5 to 72% among community-dwelling women [3]. Over all age groups, SUI is most common (49%), followed by mixed urinary incontinence (MUI), 29%, and UUI, 21% [4]. With the support of the hammock theory and integral theory [19,20], sling operations such as tension free vaginal tape or Trans-obturator tape seem to be very effective treatment for SUI [21-23]. In MUI, sling operations can effectively treat stress incontinence. Surgical effectiveness is limited in UUI or OAB, with behavior therapy, bladder training, and anticholinergic drugs the mainstay of treatments. In refractory cases, there are several options such as sacral neuromodulation, intravesical botulinum toxin injections, and bladder augmentation. However, these are invasive and patients are reluctant to be treated. The cause of UUI is presumed to be the bladder abnormality itself or neurologic abnormality. The lower urinary tract is innervated by three sets of peripheral nerves (the parasympathetic, sympathetic, and somatic nervous systems), and contains afferent and efferent motor axons [9,24]. Pelvic parasympathetic nervous system

Table 2. Parameters of heart rate variability for group A and group B

	Group A - non-DO (n = 53)	Group B - DO (n = 12)	P-value
SDNN (ms)	32.0 ± 17.2	35.3 ± 27.4	0.605
RMSSD (ms)	24.7 ± 20.0	18.3 ± 13.6	0.291
HR (bpm) [a]	75.1 ± 10.7	92.3 ± 56.1	0.040
TP (ms^2)	836.0 ± 1,059.3	770.3 ± 943.5	0.844
VLF (ms^2)	437.9 ± 478.0	583.9 ± 888.4	0.427
LF (ms^2)	206.9 ± 331.8	111.9 ± 126.3	0.335
HF (ms^2)	191.1 ± 397.5	74.5 ± 140.9	0.323
LF/HF ratio [a]	1.9 ± 1.9	4.3 ± 3.8	0.003

Values are presented as mean ± SE.
DO, detrusor overactivity; SDNN, standard deviation of the N-N interval; RMSSD, square root of the mean squared differences of successive N-N intervals; HR, heart rate; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency.
[a] P < 0.05 by Mann-Whiney U test.

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originates from sacral region (S2-4) and contracts bladder, relaxes urethra. Sympathetic nervous system, originates from thoracolumbar region (T11-L2), relaxes bladder, contracts bladder base and urethra. Somatic nervous system which innervates external urethral sphincter is delivered via pudendal nerve originate from sacral region (S2-4). This modulation of autonomic and somatic nervous system can induce normal voiding, and autonomic nervous system plays an important role in regulating bladder function [7].

Afferent nerve from pelvic, hypogastric and pudendal nerve sends information from lower urinary tract to lumbar and sacral cord [7,8]. Afferent nerve in pelvis contains capacity and contractility amplitude of bladder, composed of myelinated Aδ and unmyelinated C nerve fiber. Normal voiding is accomplished by myelinated Aδ nerve fiber in response to expansion of bladder. But neurological abnormality, inflammation, cold stimuli can stimulate unmyelinated C fibers and cause urge urinary incontinence and bladder pain [7,25].

The cause of hypersensitivity of bladder related to UUI is thought to be in the neurogenic or myogenic reason [2,26], neurogenic mechanism is occurred to develop unstable contraction of bladder on abnormal activation of voiding reflex [2]. As cyclic storage and excretion of urine in lower urinary tract is controlled by neural circuit in brain, spinal cord and peripheral ganglion, bladder instability and urinary incontinence could be evoked by abnormality in neural control mechanism of lower urinary tract by central nervous system and peripheral nervous system. Myogenic mechanism of bladder hypersensitivity is caused by malfunction of detrusor smooth muscle [26]. During storage phase, bladder regularly and actively controls bladder function, which is called autonomous function and it is related to local contraction and relaxation of bladder wall and that is controlled by detrusor muscle.

It is difficult to explain neurogenic and myogenic mechanism separately because of close and reciprocal relationship between them. The cause of this bladder hypersensitivity can be classified by loss of central, peripheral inhibitory mechanism, increase of afferent stimuli from lower urinary tract, develop of bladder reflex pathway resistant to central inhibitory mechanism and increased excitatory stimuli in micturition reflex [2].

Various models have been developed to explain the pathophysiology of bladder hypersensitivity. When patient has spinal cord injury, lower urinary tract obstruction, demyelization disease, Parkinson's disease, interstitial cystitis, diabetes mellitus, multiple sclerosis and aging etc., bladder hypersensitivity is presented. Characteristically, these disease show that long term change of smooth muscle induce neurologic change. Recently, it is thought that growth factors influence the accommodation of neural pathway associated with voiding dysfunction in a long term [7]. And exchange of information between muscle and urothelium is done by neurotransmitter, prostaglandins, and various growth factors. Dysfunction of nerve, smooth muscle and urothelium altogether induce OAB and UUI [25].

From this point of view, it has been postulated that abnormality of ANS could increase overactivity of bladder and induce urge incontinence and voiding dysfunction can relate to the autonomic nervous system, particularly for storage symptoms [27].

HRV is a new, important tool for studying autonomic dysfunction [28,29]. It is known that HRV is the most useful and simplest method to evaluate the function of ANS *in vivo*, and is frequently used to evaluate the function of ANS due to the action of sympathetic and parasympathetic nervous system on HRV [30,31]. Also HRV is a strong, independent predictor of mortality following acute myocardial infarction [32-34]. The variation of instantaneous heart rate is a physiologic phenomenon that reflects autonomous control on the sinusal node [16]. LF variations reflect baroreflex activity, which modulates sympathetic and parasympathetic outflow to the sinusal node. HF variations are due to respiratory sinus arrhythmia, which is under control of the parasympathetic nervous system [15].

HF and RMSSD are predominantly responses to changes in parasympathetic tone, whereas LF and SDNN are dually influenced by cholinergic and adrenergic activities, as well as by other physiologic inputs. The LF to HF ratio reflects the balance between the two components of the ANS. A ratio of less than 1 means that parasympathetic activity is predominant and a ratio of greater than 1 means that sympathetic activity is predominant. The values of TP are similar to those of SDNN.

In order to standardize physiological and clinical studies, some investigators [28] have suggested that short-term recordings of 5-minute be made under physiologically stable conditions processed by frequency-domain methods, and/or they have suggested that nominal 24-hour recordings be processed using time-domain methods. Experience shows that a substantial part of the long-term HRV value is attributable to day-night differences. Thus, long-term recordings need to be analyzed using time-domain methods. We conducted a short study because 24-hour electrocardiographic recording would have limited our ability to compare the HRV results obtained during varying activities, such as exercise, sleep, and deep breathing.

In this study we found that the mean values of LF, HF, SDNN and RMSSD were lower in patients with detrusor activity, but not significantly. The LF to HF ratio was significantly higher in patients with UUI or detrusor overactivity. Decreased HF and RMSSD suggest decreased parasympathetic tone, and decreased LF indicates decreased parasympathetic tone. Similarly, LF and RMSSD were lower in patients with UUI than SUI patients, suggesting decreased sympathetic tone. The LF to HF ratio was also significantly higher in patients with UUI than SUI, DO than non-DO which means UUI or DO patients have relatively high sympathetic activity than parasympathetic activity.

This result is met with the previous study which reported parasympathetic activity in women with OAB were lower than in healthy women [9]. Similarly, Hubeaux at al found a different autonomic balance in response to bladder filling in the SUI and OAB groups. Elsenbruch and Orr [35] reported that the value of LF in diarrhea-domain irritable bowel syndrome (IRB) patients was increased than that of constipation-domain IRB patients. Most investigators believe that the mechanism of OAB is similar as diarrhea-domain IRB, we suggest that relative sym pathetic activity can be a causative factor of UUI and IRB.

Major ANS dysfunction usually reflects relative sympathetic hyperactivity, which may be important in patients with voiding dysfunction, especially with dominant storage symptoms. HRV parameter was similar between women with SUI and OAB but the balance between the two components of the ANS (LF as sympathetic activity and HF as parasympathetic activity) in response to bladder filling was different in the two groups. So, the ANS imbalance (increase in sympathetic activity at the end of bladder filling, concomitant with a decrease in parasympathetic activity) could be involved in the pathophysiology of idiopathic OAB [11], which is compatible with the result of this study.

The current study has several limitations. First, it is a retrospective study, not randomized control. Second one is that the number of including subjects who have DO proven by urodynamic study is small. Third, we divided patients into two groups according to the presence of detrusor overactivity, but the existence of detrusor overactivity could not be detected by urodynamic study even in the patients who have DO actually.

In conclusion, our study suggests that ANS dysfunction, especially an imbalance between sympathetic and parasympathetic activity, could contribute to UUI and detrusor overactivity. This relationship between ANS dysfunction and bladder dysfunction should be expanding in further studies.

This study shows different status of ANS in patients with UUI from SUI, DO from non-DO.

Increased LF/HF values indicate relative sympathetic hyperactivity versus parasympathetic activity. Changing ANS activity could be an indicator of UUI and may be related to DO.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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