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Autonomic dysfunction and arterial stiffness in female overactive bladder patients and antimuscarinics related effects☆

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ABSTRACT

Objectives: To investigate the characteristics of autonomic function and arterial stiffness of OAB women, their relations with urodynamic parameters, and the impact of antimuscarinics on the above parameters.
Study design: A total of 85 OAB women and another 65 women without OAB were selected. Forty-two OAB women who enrolled before March 2009 were treated with tolterodine for 12 weeks, and another 43 OAB women who enrolled thereafter were treated with solifenacin.
Main outcome measures: The differences of the heart rate variability, cardio-ankle vascular index (CAVI) and ankle-brachial pressure index (ABI) between OAB and asymptomatic women, and their changes after 12 weeks' antimuscarinics for OAB women.
Results: OAB women had higher low frequency/high frequency ratios (LF/HF) (OAB: 1.5 ± 1.1 vs. the control: 1.1 ± 0.7, $P = 0.04$). Nonetheless, CAVI and ABI did not differ between OAB and the control group. The square root of the mean squared differences of successive NN intervals (RMSSD) is associated with nocturia (Spearman's $\rho = 0.23$, $P = 0.049$), LF is associated with urgency episodes (Spearman's $\rho = 0.28$, $P = 0.01$), and maximum urethral closure pressure is negatively associated with CAVI (Spearman's $\rho = -0.26$, $P = 0.02$). After 12 weeks' treatment, a decrease of RMSSD, HF, CAVI and an increase of LF/HF were found in the tolterodine group but not in the solifenacin group.
Conclusions: OAB women have higher severity of autonomic dysfunction with sympathetic predominance. Tolterodine may improve arterial stiffness but may deteriorate autonomic dysfunction to more sympathetic predominance. Thus, tolteridine should be used for OAB with caution in women with preexisting symptoms of autonomic dysfunction.

1. Introduction

Overactive bladder syndrome (OAB), with or without urge incontinence, is characterized by urinary urgency, frequency, and nocturia [1]. Myogenic, neurogenic, and peripheral autonomous mechanisms have been used as the possible etiologies of detrusor overactivity, a frequently seen urodynamic finding in OAB patients [2]. However, the exact etiology of OAB is still obscure.

The overall prevalence of overactive bladder is 16.9% in women [3]. Higher prevalence of cardiovascular comorbidities, such as ischemic heart disease and cerebral vascular disease, in OAB women has been reported [4]. Autonomic dysfunction is associated with higher cardiovascular risk [5]. It has been reported that autonomic dysfunction may be associated with OAB women but with conflict results [6,7]. Choi et al. reported a decrease in parasympathetic activity in OAB women [6]. However, a higher parasympathetic activity was found in OAB women with empty bladder in the report of Hubeaux et al. [7]. Thus, the aim of this study is to delineate the autonomic pattern of OAB women, and its association with urodynamic features.

In the Women's Health Initiative Observation Study, 42.4% of the participants (their ages were between 50 and 79 at baseline) had a history of hypertension and 2.0% reported peripheral arterial disease [8]. Many OAB women were within the above age range [9]. Thus, we are interested whether OAB women have higher severity of peripheral arterial disease, and whether antimuscarinics is detrimental to peripheral arterial condition. In this study, arterial

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stiffness and low extremities atherosclerosis, which were associated with higher cardiac risk, were measured as a surrogate for the peripheral arterial condition [10,11].

A variety of antimuscarinics remain the mainstay therapy for OAB. Tolterodine shows a similar degree of selectivity for all muscarinic receptor subtypes, and solifenacin has a moderate selectivity for the M3 receptor over the M2 receptor [12]. We have reported that tolterodine has a greater effect in increasing heart rate than solifenacin [12]. We are also interested whether tolterodine and solifenacin have different autonomic influences. Thus, the aims of this study are to investigate (1) the autonomic function and the peripheral arterial condition of OAB women, and their associations with urodynamic parameters, (2) the impact of antimuscarinics on the autonomic function and peripheral arterial condition, and (3) if there are any difference of treatment related effects between tolterodine and solifenacin.

2. Methods

The Research Ethics Committee of the hospital approved the study protocol. Informed consent was obtained from each participant. This clinical trial was a non-randomized open-label design study, conducted from August 2008 to January 2010 at the department of Obstetrics and Gynecology of the National Taiwan University Hospital.

The screening visit was designated as visit 0, and the inclusion criteria included: (1) women of at least 18 years of age who had at least a 3-month history of OAB symptoms, including urgency, urinary frequency, nocturia or urge incontinence; and, (2) an average of $\geq$8 micturitions per 24-hour period. Eligibility was determined at visit 1 (baseline, one week after visit 0), using the results recorded in the 3-day bladder diary prior to visit 1. Urodynamic studies were also performed before visit 1 and after 12 week's treatment. Solifenacin became available after March 2009 at the National Taiwan University Hospital. The women who enrolled before March 2009 were treated with tolterodine 4 mg SR. Owing to the availability of solifenacin in the hospital since March 2009 and our interest about the difference in effect between tolterodine and solifenacin, the women who enrolled after March 2009 were treated with solifenacin 5 mg once a day for 12 weeks. Patients were followed-up at week 4 (visit 2), week 8 (visit 3), and week 12 (visit 4). All of the women with OAB were asked to complete a validated Chinese version of the Overactive Bladder Symptom Score (OABSS) questionnaire [13] and the short form of the Incontinence Impact Questionnaire (IIQ-7) [14], a standard 12-lead electrocardiography, 15 min of Holter monitoring, cardio-ankle vascular index (CAVI) and ankle-brachial pressure index (ABI) measurements at visit 1 (before treatment) and at visit 4. Women without OAB and history of cardiovascular disease (such as ischemic heart disease and cerebral vascular disease) were also invited as the control group and complete the above questionnaires and undergo all of the tests except urodynamic studies and pad testing.

3. Heart rate variability (HRV) measurements

HRV was measured using a continuous ambulatory Holter electrocardiographic recorder (model 3100 A, Philips Medical System, Andover, Massachusetts) with a sampling rate of 250 Hz (4 ms) after emptying the bladder and resting for 30 min. The electrocardiographic signals were recorded for 15 min. The QRS complexes were automatically classified and manually verified as normal sinus rhythm, atrial or ventricular premature beats, or noise by comparison with adjacent QRS morphology. The R–R intervals were deduced from the adjacent normal sinus beats, and their interval time series were processed by a program written in the Matlab language (version 5.2, The Mathworks Inc., Natick, MA, USA) [15].

We obtained the time domain parameters, including the standard deviation of the normal-to-normal (NN) intervals (SDNN) and the square root of the mean squared differences of successive NN intervals (RMSSD). SDNN is an estimate of overall HRV; and RMSSD is an estimate of high-frequency variations in heart rate [16].

We also obtained the frequent domain parameters, including total power, very low frequency (VLF), low frequency (LF), high frequency (HF), and the LF/HF ratio. We calculated our power spectral density by the nonparametric method (i.e., the fast Fourier transform algorithm). The efferent vagal activity is a major contributor to the HF component. LF component is considered as a marker of sympathetic modulation or both sympathetic and vagal influences [16].

4. CAVI and ABI measurements

Arterial stiffness was measured by the CAVI with the VaSera VS-1000 vascular screening system (FuKuda Denshi Co., Ltd., Tokyo, Japan) [17,18]. CAVI is a new index of arterial stiffness and independent to blood pressure, which is compatible with conventional aortic pulse wave velocity. The procedure was performed as follows: after the participants sat and rested for at least five minutes, the measurements were taken with the patients in the supine position, with monitoring cuffs attached to the right or left upper arms and ankles to detect the brachial and pulse waves; heart sounds and electrocardiograms were monitored; the pulse wave velocity from the heart to the ankle was calculated by measuring the length from the aortic valve to the ankle and dividing it by time, which was determined according to the heart sounds and the rise of the brachial and ankle pulse waves; blood pressure was also measured at the brachial artery [19]. Thus, the CAVI can be calculated by the equation: $a[(2\rho/\Delta P) \times \ln(\mathrm{Ps/Pd})\mathrm{PWV2}] + b$ (a and b: constants; PWV, cardio-ankle pulse wave velocity; ΔP, Ps-Pd; ln, natural logarithm; Pd, diastolic blood pressure; Ps, systolic blood pressure; ρ, blood density) [17,18]. The average of the left and right CAVI values was used for analysis.

The ABI, an indicator of lower extremities atherosclerosis, was also measured using the above device with cuffs that can simultaneously measure blood pressure levels in both arms and both legs. The ABI was calculated separately for each leg, and the lower of the two ABI values was used for analysis [20].

All terminology used in this paper conforms to the standards recommended by the International Urogynecological Association and International Continence Society joint report [1]. STATA software (Version 11.0; StataCorp, College Station, Texas, USA) was used for statistical analyses. The Shapiro–Wilk W test is calculated for the test of normal distribution. Wilcoxon rank-sum, signed-rank tests and linear regression analysis were used as the statistical methods where appropriate. A P value of less than 0.05 was considered statistically significant.

5. Results

Eighty-five OAB women and 65 women without OAB were enrolled in this study. The baseline characteristics of both groups are shown in Table 1. Compared with the control group, OAB women have higher LF/HF (Table 1 and Fig. 1a).

Correlations between baseline values of OAB women revealed that RMSSD was associated with nocturia (Spearman's $\rho = 0.23$, $P = 0.049$), LF was associated with urgency episodes (Spearman's $\rho = 0.28$, $P = 0.01$), and maximum urethral closure pressure was negatively associated with CAVI (Spearman's $\rho = -0.26$, $P = 0.02$).