

## CARDIOVASCULAR FUNCTIONAL ASSESSMENT IN FEMALE OVERACTIVE BLADDER PATIENTS AND THEIR CHANGES AFTER TOLTERODINE VERSUS SOLIFENANCIN TREATMENT

### Hypothesis / aims of study

To investigate the treatment-related cardiovascular effects associated with antimuscarinic drug for female overactive bladder syndrome (OAB).

### Study design, materials and methods

Eighty-one female OAB patients and 71 non-OAB women were prospectively enrolled at the outpatient clinic of Department of Obstetrics and Gynecology of National Taiwan University Hospital between August 2008 and February 2010. Forty-four patients received solifenacin (Vesicare 5mg per day) treatment, and 37 received tolterodine (Detrusitol SR 4 mg per day). All OAB female patients were asked to complete OABSS, UDI-6&IIQ-7, standard 12-leads electrocardiography (ECG), 20-minutes Holter monitoring [1], cardio-ankle vascular index (CAVI) test [2,3] before and after 12-week treatments. The above parameters were compared between OAB and non-OAB subjects, and also before and after treatments.

### Results

Female OAB patients had higher right and left CAVI values ( $p = 0.02$  and  $0.03$ , respectively) and higher low frequency/high frequency ratio ( $p = 0.02$ ), compared with non-OAB women (Table 1). In tolterodine group, right CAVI value (mean  $-0.3$  vs  $0.0$ ,  $p = 0.03$ ), the square root of the mean squared successive differences of normal to normal (NN) intervals ( $-6.9$  vs  $-0.3$  ms,  $p = 0.004$ ), the proportion of differences between successive NN intervals that are greater than 50 ms ( $-3.3$  vs  $2.2$  ms,  $p = 0.01$ ), and high frequency ( $-55.0$  vs  $-6.1$  ms<sup>2</sup>,  $p = 0.003$ ) decreased significantly, and low frequency/high frequency ratio ( $0.9$  vs  $0.0$ ,  $p = 0.0004$ ) increased significantly than solifenacin treatment (Table 2).

### Interpretation of results

Compared with non-OAB female patients, OAB patients had higher arterial stiffness and a shift of sympathovagal imbalance toward a sympathetic predominance. Besides, tolterodine treatment significantly decreased arterial stiffness, overall heart rate variability and parasympathetic activity, and shifted the imbalance toward sympathetic predominance, compared with solifenacin treatment.

### Concluding message

Female OAB patients had higher arterial stiffness and a sympathovagal imbalance toward a sympathetic predominance. Compared with solifenacin, tolterodine treatment had a significantly larger impact on the arterial stiffness and heart rate variability in patients.

Table 1. Comparisons of baseline clinical characteristics and cardiovascular function assessment between case and control groups

Variable	Control (n = 71)	OAB (n = 81)	P*	Tolterodine (n = 37)	Solifenacin (n = 44)	P**
Age (years)	55 (42-58)	53 (46-59)	0.43	56 (52-64)	52 (46-59)	0.93
Parity	2 (1-2)	2 (2-3)	0.001	2 (2-3)	2 (2-3)	0.31
Body mass index (kg/m <sup>2</sup> )	22.8 (21.0-23.8)	23.9 (21.1-26.6)	0.04	23.2 (20.4-26.6)	24.2 (22.4-26.7)	0.07
PR (msec)	159 (150-166)	161 (148-169)	0.77	162 (146-169)	160 (150-171)	0.43
QT (msec)	373 (352-392)	374 (358-398)	0.40	376 (359-404)	373 (358-391)	0.52
QTc (msec)	400 (387-411)	403 (390-418)	0.39	404 (389-417)	398 (391-419)	0.82
Right CAVI	8 (7.3-8.7)	8.3 (7.7-9.2)	0.02	8.4 (7.9-9.2)	8.3 (7.5-9.1)	0.58
Left CAVI	7.9 (7.3-8.5)	8.2 (7.6-9.0)	0.03	8.3 (7.8-8.9)	8.0 (7.5-9.1)	0.46
SDNN (msec)	34.4 (28.0-46.4)	35.6 (26.0-43.6)	0.59	35.1 (25.9-43.9)	36.4 (26.5-42.7)	0.86
RMSSD (msec)	24.5 (19.2-33.0)	23.9 (17.1-30.5)	0.37	27.2 (17.7-31.2)	22.2 (15.3-30.1)	0.55
pNN50 (msec)	3.8 (0.8-11.4)	3.3 (0.5-8.2)	0.43	4.1 (0.8-8.0)	2.1 (0.4-8.2)	0.66
VLF (msec <sup>2</sup> )	348 (189-553)	299 (153-507)	0.58	295 (143-482)	308 (159-504)	0.65
LF (msec <sup>2</sup> )	120 (64-209)	109 (67-179)	0.63	102 (60-150)	123 (69-180)	0.30
HF (msec <sup>2</sup> )	126 (65-221)	116 (52-175)	0.11	116 (56-183)	115 (49-172)	0.86
TP (msec <sup>2</sup> )	561 (366-1096)	596 (304-879)	0.37	538 (313-891)	615 (310-855)	0.74
LF/HF	0.84 (0.57-1.29)	1.18 (0.70-1.90)	0.02	0.91 (0.64-1.69)	1.27 (0.86-1.89)	0.10

1. Data are expressed as median (25–75% interquartile range)

2. \*By Wilcoxon rank-sum test (control vs. OAB group), \*\* By Wilcoxon rank-sum test (Tolterodine vs Solifenacin group)

3. CAVI: cardio-ankle vascular index; HF: high frequency; LF: low frequency; LF/HF: LF/HF ratio; pNN50: the proportion of

differences between successive NN intervals that are greater than 50 ms; PR: PR interval in electrocardiography; QT: QT interval in electrocardiography; QTc: corrected QT interval; RMSSD: the square root of the mean squared successive differences of normal to normal (NN) intervals; SDNN; standard deviation of normal to normal RR intervals; TP: total power; VLF: very low frequency

Table 2. Comparisons of changes from baseline data between tolterodine and solifenacin group

Variable	Tolterodine (n = 37)	Solifenacin (n = 44)	P*
PR (msec)	0.3(-4.4, 5.1)	1.9 (-0.4, 4.3)	0.32
QT (msec)	-2.7 (-12.2, 6.9)	4.3 (-1.9, 10.5)	0.06
QTc (msec)	8.4 (-0.8, 17.7)	1.0 (-5.7, 7.7)	0.53
Right CAVI	-0.3 (-0.5, -0.1)	0.0 (-0.2, 0.2)	0.03
Left CAVI	-0.2 (-0.5, -0.02)	0.0 (-0.3, 0.2)	0.07
SDNN (msec)	-4.5 (-9.9, 0.9)	-3.9 (-9.2, 1.5)	0.44
RMSSD (msec)	-6.9 (-10.4, -3.5)	-0.3 (-4.5, 3.9)	0.004
pNN50 (msec)	-3.3 (-6.6, 0.1)	2.2 (-1.8, 6.3)	0.01
VLF (msec <sup>2</sup> )	3.6 (-198.9, 206.2)	-116.7 (-261.5, 28.1)	0.82
LF (msec <sup>2</sup> )	-20.8 ( -76.8, 35.3)	-38.8 (-80.3, 2.7)	0.78
HF (msec <sup>2</sup> )	-55.0 (-86.2, 23.8)	-6.1 (-66.5, 54.4)	0.003
TP (msec <sup>2</sup> )	-72.0 (-304.0, 160.0)	-161.5 (-372.4, 49.3)	0.68
LF/HF	0.9 (0.5, 1.3)	0.0 (-0.4, 0.5)	0.0004

1. Data are expressed as mean (95% confidence interval)

2. \*By Wilcoxon rank-sum test.

3. Abbreviations as in Table 1.

#### References

1. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standard of measurement, physiological interpretation and clinical use. *Circulation* 1996;93:1043-65
2. Huang CL, Chen MF, Jeng JS, et al. Postchallenge hyperglycaemic spike associate with arterial stiffness. *Int J Clin Pract* 2007;61:397-402
3. Yambe T, Yoshizawa M, Saijo Y, et al. Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). *Biomed Pharmacother* 2004;58(Suppl 1):S95-8

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<b>Is this a clinical trial?</b>	<b>Yes</b>
<b>Is this study registered in a public clinical trials registry?</b>	<b>No</b>
<b>Is this a Randomised Controlled Trial (RCT)?</b>	<b>No</b>
<b>What were the subjects in the study?</b>	<b>HUMAN</b>
<b>Was this study approved by an ethics committee?</b>	<b>Yes</b>
<b>Specify Name of Ethics Committee</b>	<b>National Taiwan University Hospital Research Ethics Committee</b>
<b>Was the Declaration of Helsinki followed?</b>	<b>Yes</b>
<b>Was informed consent obtained from the patients?</b>	<b>Yes</b>