A noninvasive evaluation of autonomic nervous system dysfunction in women with an overactive bladder

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1. Introduction

The overactive bladder (OAB) syndrome was defined by the International Continence Society as “urinary urgency, with or without urinary incontinence, usually with frequency and nocturia,” in the absence of local infection or other pathologic changes [1]. This syndrome, which affects 33 million adults in the United States, or approximately 16.5% of the population [2,3], results in a lower quality of life and in treatment costs similar to those faced by women with osteoporosis or gynecologic cancers [4]. There are several theories for the cause of OAB, which may not be mutually exclusive [3,5–8]. Some are based on the observation of an abnormally high parasympathetic activity, whether at the level of the epithelial cells of the bladder, which can release acetylcholine inappropriately, or in the parasympathetic fibers of the muscular layer of the body of the bladder (or bladder detrusor muscle) [3,7]. In persons with OAB, the parasympathetic fibers that cause the detrusor to contract for urination remain stimulated after the bladder has emptied, which causes the bladder to contract again before it is full; and these fibers are part of the autonomic nervous system (ANS).

Quantifying the severity of this parasympathetic overactivity is difficult with the current methods. The overactive bladder symptom score (OABSS), which goes from 0 to 15, is subjective and therefore has limitations, and urodynamic investigations can be invasive and are time consuming [9,10]. There is a need for a reliable, objective, and noninvasive method of measuring the activity of the nerve fibers that control the urge to urinate (or micturition) and urination.

A direct relationship between heart rate variability (HRV) and parasympathetic effects has been reported [11,12], including in studies focusing on women with OAB or urinary stress incontinence [13] or children with monosymptomatic nocturnal enuresis [14]. Moreover, Akselrod et al. [15,16] have demonstrated that sympathetic and parasympathetic functions can be evaluated by performing spectral density (PSD) analyses of HRV. The aim of the present study was to: (1) quantify HRV data; (2) display the obtained values by means of 3-D spectrograms and multiscale entropy graphs; and (3) examine the values and displays for study patients and controls, as differences would indicate disturbances in ANS activity in women with OAB.

2. Materials and methods

The study was carried out from January 2004 through December 2006 with 33 women between 30 and 60 years of age seen for OAB at the outpatient clinic of the Department of Obstetrics and Gynecology of Taiwan Adventist Hospital and 176 age-matched women without OAB who acted as controls. The study patients met the criteria for OAB as defined by the 2003 International Incontinence Society criteria [1] or had an OABSS score greater than 8. All had previously provided a medical history questionnaire and parasympathetic effects has been reported [11,12], including in studies focusing on women with OAB or urinary stress incontinence [13] or children with monosymptomatic nocturnal enuresis [14]. Moreover, Akselrod et al. [15,16] have demonstrated that sympathetic and parasympathetic functions can be evaluated by performing spectral density (PSD) analyses of HRV. The aim of the present study was to: (1) quantify HRV data my means of PSD analyses for all participants; (2) display the obtained values by means of 3-D spectrograms and multiscale entropy graphs; and (3) examine the values and displays for study patients and controls, as differences would indicate disturbances in ANS activity in women with OAB.

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other drugs known to disrupt ANS activity, as well as women with such conditions as coronary heart disease, a neurologic disease, diabetes, a history of pelvic surgery (including hysterectomy), or any other condition known to disrupt ANS activity. Each prospective participant also underwent a physical examination, an ECG, a urinalysis, a uroflowmetry evaluation, and an ultrasound examination of the pelvis. Those with abnormal screening results were excluded.

Of 40 women with OAB, 33 were included in the study group; and of 300 prospective controls, 173 were included in the control group. The study was approved by the Taiwan Adventist Hospital Institute Review Board and all participants gave informed consent.

A noninvasive, uninterrupted procedure was used to record spontaneous voiding, a process reflecting local ANS function. Each participant drank between 500 and 1000 mL of water and ECG electrodes were placed on the precordial area. When the participants expressed a need to urinate, they were requested to hold their urine for at least 3 minutes, and then to urinate in a standard urocytometry chair while a continuous recording of the PQRS complex was made at 1000 Hz for the 3 minutes or more before voiding, during voiding, and for 5 minutes following voiding. The amount of urine voided and the flow rate were recorded, and the values were entered in a database. After voiding, an ultrasound scan of the bladder was performed to determine the volume of residual urine.

The ECG data were converted into HRV data using SPSS software, version 14 (SPSS Inc, Chicago, IL, USA). Results were expressed as mean ± SD. The Mann-Whitney U test, the Wilcoxon Signed-Rank test, and the Z test were used to compare electrophysiologic findings between study and control group; relationships were assessed using the Pearson or the Spearman rank correlation coefficient, as appropriate [17]. P < 0.05 was considered significant.

The software program Mathworks Matlab version 7 (R2009a) (The MathWorks, Natick, MA, USA) was used for the PSD analyses of HRV and to generate 3-D spectrograms and multiscale entropy graphs [18,19]. Each of the 3 datasets obtained is the result of a different mathematical approach to quantifying and displaying HRV data, and therefore ANS activity. Each provides a specific fingerprint that distinguishes individuals with or without OAB. The entropy graphs showing the normalization (or lack of normalization) of neuron signals following urination were built with values explained by the Hilbert-Hwang transform equations [20]:

\[ Z(t) = \sum_{j=1}^{n} a_j(t) e^{2\pi i f_j t} dt \quad h(o) = \frac{1}{T} \int_{0}^{T} H(o, t) dt \]

### 3. Results

The uroflowmetry results of the study patients are shown in Table 1. The women with OAB had a lower bladder capacity than the controls. A volume of 75 mL of urine was sufficient to induce micturition in the women with OAB whereas the controls required 400 to 500 mL of urine.

The PSD analyses of HRV revealed differences between the OAB and control groups. Some measurements in the time domain were significantly lower in the OAB group (P < 0.05). In the frequency domain, total power [or variance, which distributes as a function of frequency [21]], as well as very low frequency (VLF) and high frequency (HF) peaks—those representing parasympathetic activity—were significantly different in the 2 groups (Table 1 and Fig. 1).

Fig. 1 represents the HRV values for the study and control group, with 95% confidence interval (as darker bars) and range. The values were significantly lower in the OAB group.

In Fig. 2, 3-D spectrograms with a time axis (Y axis), an intensity axis (Z axis), and a frequency axis (X axis) display HRV values gathered over the entire ECG recording session for a participant with OAB and a control (the recording began before the onset of micturition and ended 5 minutes after urination). Values for the frequency peaks of the spectrum and for spectral density power are shown in the tables below the spectograms, and the value for the high-frequency peak is much higher for the participant with OAB. Differences are easier to distinguish on 3-D spectrograms than on ECG tracings. For the participant without OAB, strong low-frequency (LF), 0.1-Hz spikes can be seen for the first 300 seconds as she resisted an urge to void and retained her urine inside the bladder. At about 300 seconds she was allowed to void, and the intensity of the 0.1-Hz spikes decreased sharply (Fig. 2a). In contrast, the spectrogram shows values as irregular and random for the participant with OAB (Fig. 2b).

In Fig. 3, 3-D spectrograms display HRV values following urination for a participant without OAB (Fig. 3a) and a participant with OAB (Fig. 3b). Fig. 3a shows a relatively stable balance between high and low frequencies, with no high-frequency spikes. We calculated the LF/HF ratio, a measure of the balance between sympathetic and parasympathetic neuronal activity. It was 1.43 in the participant without OAB, indicating a good balance. In contrast, in Fig. 3b, the aspect of the spectrogram and the LF/HF ratio of 0.16 both indicate an elevated high-frequency neuronal activity. Figs. 2 and 3 each show a greater mean parasympathetic nerve stimulation in an OAB patient.

Multiscale entropy graphs for a participant without OAB (Fig. 4a) and a participant with OAB (Fig. 4b) are shown in Fig. 4. There are clear differences between the graphs, with a beginning, a process, and a return to baseline only for the participant without OAB.

The results for the participants whose results we described were similar to the results for the other participants in the same groups. We used 2 methods of displaying HRV values after they were transformed by PSD analysis, 3-D spectrograms and multiscale entropy graphs showing the normalization (or lack of normalization) of neuron signals following urination, and they both presented differences between study and control group in a way that made ANS disturbances obvious in the women with OAB.

### 4. Discussion

The bladder is a smooth-muscle organ attached to a nerve. Two hypotheses have been brought forward to explain the pathophysiology of OAB. The first is muscle related [5,6]. It proposes that changes
Fig. 1. Plots comparing HRV values for the study and control groups.
Fig. 2. 3-D spectrograms displaying HRV values for the entire ECG recording (i.e., from before the onset of micturition to 5 minutes after urination) for a participant without OAB (2a) and a participant with OAB (2b).

Fig. 3. 3-D spectrograms displaying HRV values following urination for a participant without OAB (3a) and a participant with OAB (3b).
in the cells of the detrusor are necessary for the production of an involuntary contraction, and that a partial denervation of the detrusor might increase the excitatory potential between muscle cells, thereby changing the properties of the muscle. It further proposes that a contraction occurring in any part of the detrusor would spread through the entire muscle.

The second hypothesis is neurogenic [8]. It proposes that damage to inhibitory pathways in the brain or spinal cord can trigger detrusor overactivity. Inhibition of micturition occurs in a center located in the rostral pons, and a brain injury can induce detrusor overactivity by damaging this center. An injury to the spinal cord can induce detrusor overactivity by suppressing the mechanisms that activate the sympathetic and somatic inhibition of parasympathetic activity in the bladder. Persons with a history of cerebrovascular events or Parkinson's disease can also have OAB for neurogenic reasons [3]. Moreover, acetylcholine is released in excessive amounts in persons with OAB when the bladder is filling, and neural feedback can provoke a sensation of urgency [3] before the bladder is full. There may be other causes of detrusor overactivity.

The indices analyzed in this study were SDNN (standard deviation of the normal-to-normal intervals, i.e., all intervals between adjacent QRS complexes); SDNN “reflexes all the cyclic components responsible for variability in the period of recording” [21]; RRMSSD (square root of the mean squared differences of the successive NN intervals); NN50 (number of interval differences of successive NN intervals greater than 50 milliseconds); and pNN50 (proportion obtained by dividing the value for NN50 by the total number of NN intervals) [21]. All values were significantly lower in the study group than in the control group. This may be because parasympathetic overactivation in the ANS lowered heart rate in the participants with OAB, with the consequence of decreasing HRV in these women.

Frequency analysis showed that total power, VLF range (normal range, 0.003–0.04 Hz), and HF range (normal range, 0.15–0.4 Hz) were significantly different in the 2 groups. Clinically, the HF range has been shown to represent parasympathetic activity modulated by respiration, and the LF range (0.04–0.15 Hz) to represent mainly pressure-modulated sympathetic activity [21].

In Fig. 2a, the strong 0.1-Hz spike during the 300 seconds following the onset of micturition represents the increased sympathetic stimulus needed to retain urine during urinary urgency. After 300 seconds, as the participant voided, the sympathetic stimulus decreased and a small, 0.3-Hz parasympathetic stimulus occurred. This change in ANS activity resulted from the relaxation of the urethral sphincter and the emptying of the bladder. As the decrease in sympathetic activity was sufficient to allow the bladder to empty, there was no need for a drastic increase in parasympathetic activity. In contrast, Fig. 2b shows a disorganized pattern of sympathetic and parasympathetic activity before, during, and after urination. The combination of unsustained sympathetic and uncontrolled parasympathetic discharges made urine retention difficult. The imbalance between sympathetic and parasympathetic stimulations resulted in uncoordinated activity even 800 seconds after voiding. The 3-D spectrogram in Fig. 2b provides graphic evidence of ANS dysfunction.

In Fig. 3a, there is a stable balance between sympathetic and parasympathetic stimulation following urination. Since the LF/HF ratio was 1.43, the marginal bias toward a sympathetic stimulus points to a sympathetic intensity bias at baseline. In contrast, there is a continued parasympathetic stimulation even after voiding is completed in Fig. 4b. This is evidenced by the predominance of a 0.3-Hz signal (i.e., a HF signal); by a LF/HF ratio of 0.16; and by a lower variation in heart rate following voiding. This parasympathetic hyperexcitability was clinically evident in the study patient, who felt urinary urgency even after voiding was completed.

Multiple scale entropy analysis is a new method of analyzing the complexity of biological results, even though they operate under multiple spatial and temporal scales [19]. Within the results, different points on the graph are simultaneously sampled at a specified time interval and then averaged.

We used from 2 to 20 data points simultaneously in our entropy analysis. The entropy graphs representing ANS complexity in Fig. 4 are constructed using the means of the HRV values transformed from the ECG recordings of the 176 controls and 33 study patients. We used a complexity scale rather than a time scale, but the results would be similar if moving averages had been calculated using different time scales. The results were statistically adjusted for randomness. Complexity increased during micturition for the participants without OAB, but their graph shows entropy returning very close to its baseline value after urination (Fig. 4a). The fact that randomness (or entropy) does not increase with increasing complexity implies that HRV—and therefore the ANS—is well controlled in these women. Complexity also increased during micturition for the participants with OAB, but their graph does not return within the standard deviation of the baseline value after urination (Fig. 4b). This finding suggests a disorganized ANS function consistent with parasympathetic hyperexcitability.

The tools usually used to evaluate OAB are questionnaires and a 7-day voiding diary. There is the Overactive Bladder Questionnaire (OABq); the Primary OAB Symptom Questionnaire (POSQ); and the Overactive Bladder Symptom Score (OABSS) where 3 to 5 points indicate a mild, 6 to 10 points a moderate, 11 or 12 a severe, and a score higher than 12 a very severe condition. In the 7-day voiding diary the patient records how many times per 24 hours she passes urine, the volume of urine that she passed, and the time intervals between urination. In principle, the patient's urge incontinence can be understood from these data. In practice, however, the voiding diary is too inconvenient and the questionnaires are too subjective to be very useful.

On the other hand, using HRV data is simple and noninvasive. As the need to pass urine arises after drinking water, the sympathetic innervation of the bladder is stimulated and the neural message to
pass urine is transmitted to the bladder. Once urination is completed, the parasympathetic innervation signals the relief of having passed urine. We used these physiological facts to develop a system capable of monitoring the action potential that urination provokes in nerve cells. Through simple mathematical transformations we were able to construct the graphs in Figs. 2–4, and thus quantify and visualize ANS dysfunction. Continuous ECG recording through a band-pass filter produces differential equations and mathematical square roots, of which moving averages and thresholds are derived to generate HRV data.

Our diagnostic and monitoring system would be useful not only in medical centers, where urodynamics and other invasive evaluations would no longer be needed, but also to family physicians and, especially, to the patients themselves, who could be treated without delay with the appropriate medications.

The use of continuous ECG recording to generate HRV data is a novel, noninvasive method of quantifying ANS dysfunction in persons with OAB. We have shown statistically significant differences in ANS activity between persons with and without OAB. And by showing that HRV data can be converted into PSD values, 3-D spectrograms, and MSE graphs, we have provided additional, powerful tools to quantify and visualize these differences. Further, we showed that the differences in ANS activity in persons with OAB were the result of parasympathetic hyperactivity.

Still today, the diagnosis of OAB primarily relies on the presence of urinary urgency and frequency, nocturia, and urge incontinence. We propose using HRV to evaluate ANS dysfunction and simplify treatment monitoring. It is likely that the HRV data can be converted into PSD values, 3D-spectrograms, and MSE graphs, providing additional, powerful tools to quantify and visualize differences in ANS activity. Furthermore, because these methods can also be used to monitor treatment response, they can be applied to pharmacological or surgical treatment [22,23]. And because of their noninvasiveness, these methods can also be used in children.

Conflict of interest

The authors declare that they have no conflicts of interest.

References


