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ORIGINAL ARTICLE

Alteration of Autonomic Nervous System Function in Male Patients with Overactive Bladder Syndrome

Aşırı Aktif Mesaneli Erkek Bireylerdeki Otonomik Sinir Sistemi Fonksiyon Bozukluğu

[1]Betul Banu Karasu, [2]Ahmedi Uğur Oruç

[1]Sincan Education and Research Hospital, Cardiology Clinics
[2]Etimesgut Sehit Sait Erturk State Hospital, Department of Urology

Correspondence

Betul Banu Karasu, Sincan Education and Research Hospital, Cardiology Clinics, Ankara/TURKIYE

E-Mail: benginoglu@yahoo.com

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ABSTRACT

Background/Aims: Overactive bladder is a frequently encountered urological disease that has debilitating effects on quality of life. Some hypotheses have been put forward in order to explain the main pathophysiology underlying this clinical phenomenon, however, the exact mechanism remains unclear and the relevant reports are limited in number confined to female patients, and have conflicting results. Therefore, we aimed to examine one of these hypotheses -autonomic nervous system dysfunction- in male patients with overactive bladder.
Methods: We included 41 male patients with overactive bladder and 43 healthy males in this study. Their electrocardiographic signals were recorded in the prevoiding and postvoiding periods and then converted to heart rate variability parameters which may reveal autonomic nervous system dysfunction.
Results: Standard deviation of normal-to-normal interval, square root of the mean squared differences of successive normal-to-normal intervals, low frequency signal and low frequency/high frequency ratio were significantly lower while high frequency signal was significantly higher in the patient group compared to healthy controls ($p<0.05$).
Conclusions: Heart rate variability was attenuated in male patients with overactive bladder and parasympathetic predominance was observed during both prevoiding and postvoiding periods, contrary to some of the previous reports revealing sympathetic predominance in female patients.

Key words: autonomic nervous system, electrocardiography, heart rate, male, overactive urinary bladder

ÖZ

Amaç: Aşırı aktif mesane, oldukça sık görülen ve hayat kalitesini azaltan ürolojik bir hastalıktır. Bu klinik durumun altında yatan ana patofizyolojiyi açıklayan birçok hipotez öne sürülmüştür, ancak altta yatan mekanizma tam olarak açıklığa kavuşamamıştır. Ayrıca ilgili çalışmaların sayısı oldukça sınırlı, sadece bayan hastaları kapsamakta ve çelişen sonuçlar içermektedir. Biz burada, öne sürülen hipotezlerden biri olan otonomik sinir sistemi fonksiyon bozukluğunu aşırı aktif mesanesi olan erkek hastalarda araştırmayı amaçladık.
Yöntem: Bu çalışmaya, 41 aşırı aktif mesanesi olan erkek hasta ile 43 sağlıklı erkek birey alınmıştır. Katılımcıların elektrokardiyografik sinyalleri işeme öncesi ve işeme sonrası dönemde kaydedilmiş ve otonomik sinir sistemi fonksiyon bozukluğunu gösterebilen kalp hızı değişkenliği parametrelerine dönüştürülmüştür.
Bulgular: Kontrol grubuna kıyasla, aşırı aktif mesaneli erkek hastalarda; NN intervallerinin standart sapması, ardışık normal NN intervalleri arasındaki farkların kareökü, düşük frekans bandı, düşük frekans/yüksek frekans oranı anlamlı olarak daha düşük, yüksek frekans bandı ise anlamlı olarak daha yüksek bulundu ($p<0.05$)
Sonuç: Aşırı aktif mesaneli erkek hastalarda kalp hızı değişkenliği azalmakta ve bayan hastalardaki sempatik hakimiyeti raporlayan önceki bazı çalışmaların aksine, hem işeme öncesi hem de işeme sonrası dönemde parasempatik hakimiyet gözlenmektedir.

Anahtar Kelimeler: aşırı aktif mesane, , elektrokardiyografi, erkek, kalp hızı, otonomik sinir sistemi

Introduction

Overactive bladder (OAB) is an urological disease characterized by urinary frequency, urgency and nocturia with or without urge incontinence. It is a commonly encountered clinical entity affecting 11.8% of adults and resulting in low quality of life in addition to high treatment costs. Its diagnosis is based on the exclusion of obvious pathological causes including urinary infection, malignancy, lithiasis or neurological disease (1-3). Despite its high frequency and clinical importance, the underlying pathophysiological process is not understood exactly. Two main theories, myogenic and neurogenic, have been proposed so far in order to explain a possible contributory mechanism. The first one refers to a disturbance in myoelectrical activity of the smooth muscle cells of the bladder wall spreading throughout the whole detrusor muscle. On the other hand, neurogenic theory implies an alteration in the autonomic nervous system (ANS) function which delicately regulates the continence and micturition cycle (4-6).

The relevant previous reports searching for the mechanisms that underlie the OAB were mostly designed to find out this proposed ANS dysfunction. As a result, they mainly confirmed the presence of a deterioration in ANS activity. However, the number of these reports are limited and their findings are conflicting in terms of the predominancy of sympathetic or

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Complaints: geneltip@selcuk.edu.tr

Selcuk University School of Medicine
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parasympathetic nervous system. In addition, the study population in these researches were only confined to female patients as it is established that OAB is more common in female adults (7-9). However, OAB is not a rare disease for male adults as it is encountered with a prevalence of 10.8% (1,10).

Therefore, for the first time in the literature, we aimed to investigate the ANS activity in male patients who suffer from OAB. We also tried to make a contribution to the delineation of the type of the ANS dysfunction which remains obscure. In order to detect the autonomic imbalance, we used heart rate variability (HRV) method which is a precise and noninvasive way providing both qualitative and quantitative analysis of the global ANS function (11-13).

Materials and Methods

This prospective case control study conducted between December 2022 and February 2023, included 43 male patients who had OAB and 43 healthy male individuals. For the case group, we recruited the patients who admitted to the urology outpatient clinics of our hospital and had the diagnosis of OAB while the control group was constituted of healthy subjects none of whom had urinary frequency, urgency or nocturia. The exclusion criteria involved being female, under 18 years or above 45 years of age, having urinary infection, benign prostate hyperplasia, stress induced urinary incontinence, hydronephrosis, acute/chronic renal failure, cancer, psychiatric or neurological disease, hypertension, diabetes mellitus, obesity, cardiac failure, coronary artery disease , moderate or severe heart valve disease, electrocardiogram anomalies and drug usage including beta receptor agonists, beta receptor antagonists, anticholinergics, alpha adrenergic antagonists or type A botulinum toxin injection to detrusor muscle.

Each participant underwent a detailed history taking, physical examination, complete blood count, serum glucose, urea, creatinine, electrolyte, liver enzyme examination, urinalysis, electrocardiogram and transthoracic echocardiography. All patients were asked to fill in the overactive bladder symptom score questionnaire and bladder diary in addition to the uroflowmetry and urinary system ultrasonography carried out for each patient. The overactive bladder symptom score questionnaire was used to determine the severity of OAB as well as the identification of patients with OAB (14). The diagnosis of OAB was made if the patients met the criteria stated in the International Continence Society (15). All participants refrained from smoking, drinking tea, coffee or alcohol 3 hours prior to the test since these products may alter the HRV.

Study protocol

The participants were asked to rest on a comfortable chair for 10 minutes before the test began and were instructed to drink 1000 to 1500 mL of water. The recordings were obtained in two different phases of 15 minutes each while the participant was breathing normally on the sitting position in a quiet room. 15 minutes of recording period was found more convenient in our study. The primary reason for this is that a minimum recording time of 5 minutes is recommended to measure HRV and we tried to guarantee a recording time in hospital conditions without a noise, premature ectopic beat, missing data or artifact. We also did not prefer long term monitoring in order to specifically obtain dynamic HRV responses of the patients to the changes in their bladder function and because it is not easy to keep patients in specified conditions during a whole day (16). Three standard surface electrodes were placed on the precordial area of each individual for the signal acquisition and continuous ambulatory Holter electrocardiographic monitoring (Cardio Scan II Premier, Powered by DM Software Inc. USA) with a sampling frequency of 256 Hz was used to calculate HRV. The first phase of the recording started when the participant indicated that he felt desire to void without fear of leakage. After completion of the first 15 minutes of recording, the participant was asked to empty his bladder and the second phase of recording took place following a resting period of 10 minutes on a comfortable chair.

The HRV analysis was made by the investigator who was blinded to the clinical states of the study groups. The QRS complexes were firstly screened and classified as an artifact, normal sinus rhythm or atrial and ventricular premature beat in order to be corrected before detection of R-wave peaks and calculation of R-R intervals. Lastly, the signals were processed and transformed into HRV parameters by time and frequency domain method of linear analysis.

Time domain analysis

a) The mean heart rate

b) Standard deviation of normal-to-normal (N-N) interval (SDNN): It indicates an estimate of overall cyclic components responsible for HRV and is expressed in ms. Both sympathetic and parasympathetic discharges may contribute to SDNN.

c) Square root of the mean squared differences of successive N-N intervals (RMSSD): Each time difference between successive N-N intervals is calculated, squared and then the result is averaged to obtain the square root of the total. In comparison to SDNN, it is more influenced by vagally mediated changes and therefore is shown to be an estimate of the parasympathetic activity.

Frequency domain analysis: The fluctuations in heart rate are spectrally analyzed by fast Fourier transform method to obtain frequency domain variables of HRV. These include very low frequency (VLF), high frequency (HF) and low frequency powers measured in ms^2. Power indicates the amount of energy found in a spectral band.

a) Total power (TP): It is calculated by summation of all spectral bands (VLF+LF+HF) reflecting the overall autonomic activity to cope with stress.

b) VLF: This variation represents an activity between 0 and 0.04 Hz. It partly indicates the vasomotor changes, thermoregulatory mechanisms, and fluctuations in renin-angiotensin system activity. Therefore, VLF may represent the systemic stress and does not implicate any significance on short term recordings

c) HF: This peak of the spectrum varies between 0.15 and 0.40 Hz. It represents pure cardiac parasympathetic activity because it is mainly influenced by the efferent vagal activity.

d) LF: This peak of the spectrum (0.04 to 0,15 Hz) corresponds to the joint action of parasympathetic and sympathetic activity but with a sympathetic predominance. It is also associated with SDNN.

e) LF/HF ratio: This parameter reflects alterations and balance between sympathetic and parasympathetic components, being the most sensitive indicator of sympathovagal balance. LF/HF >1 implicates the predominancy of sympathetic activity while LF/HF <1 states a parasympathetic dominancy (16-18).

Statistical Analysis

Categorical variables were expressed as frequency or percentage. Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Normally distributed continuous variables were described as mean ± standard deviation while non-normally distributed continuous variables were described as median and interquartile range (IQR, range from the 25th percentile to the 75th percentile). Categorical variables were compared by χ2 test. The comparison of normally distributed continuous variables was made by independent samples T test while that of non-normally distributed continuous variables was performed by Mann-Whitney U test. Two tailed p<0.05 was considered statistically significant and SPSS statistical package (version 20.0, SPSS, Chicago, IL, USA) was used for the analysis.

Results

Of 43 male patients with OAB, two were excluded due to unwillingness to participate in the study. Therefore, 41 male patients with OAB and 43 healthy male controls were recruited for the study. Mean age of the OAB group was 35.61±7.06 while it was 36.33±6,87 in the control group. There were no significant differences between groups in terms of age, sex, body mass index and smoking habits (Table 1).

In Table 1, the HRV parameters during the prevoiding phase are compared between two groups. TP and VLF values were not statistically different between groups (p>0.05), however, SDNN, RMSSD and LF values were found significantly lower in the OAB group (30.49±11.02 vs. 38.21±11.99, p=0.003; 27.22±10.58 vs. 33.95±10.27, p=0.004; 213 [157-285.50] vs. 313 [214-393], p=0.001, respectively). Considering the HF value and LF/HF ratio, we determined that HF was higher while the LF/HF ratio was lower in the OAB group (372 [208-536] vs. 126 [91-189], p<0.001 and 0.600 [0.400-0.898] vs. 2,148 [1.754-2.892], p<0.001, respectively).

Table 2 presents the comparison of HRV parameters between two groups during the postvoiding phase. VLF values were similar between groups (p>0.05). SDNN, RMSSD, TP, LF and LF/HF ratio were significantly lower in the OAB group (35.29±10.11 vs. 44±12.02, p=0.001; 30.78±8.72 vs. 34.95±7.24, p=0.019; 888.20±215.93 vs. 1175.30±301.69, p<0.001; 164 (118.50-211.5) vs. 471 (391-617), p<0.001 and 0.475±0.262 vs. 1.802±0.878, p<0.001; respectively) while HF value was significantly higher in the OAB group (427.39±150.66 vs. 324.56±115.55, p=0.001).

Table 1: Comparison of baseline and HRV characteristics of patients and healthy controls during the prevoiding phase

	OAB Patients (n=41) (prevoiding)	Healthy Controls (n=43) (prevoiding)	P value
Age (years)	35.61±7.06	36.33±6,87	0.639
BMI (kg/m²)	25.60±2.01	26.43±1.94	0.058
Smoking (n, %)	26 (63.4%)	29 (67.4)	0.437
Heart rate (beats/min)	73.10±8.76	71.74±9,50	0.500
SDNN (ms)	30.49±11.02	38.21±11.99	0.003*
RMSSD (ms)	27.22±10.58	33.95±10.27	0.004*
TP (ms²)	1044.59±306.34	949.53±224.56	0.110
VLF (ms²)	431.02±129.22	476.30±97.12	0.072
LF (ms²)	213 (157-285.50)	313 (214-393)	0.001*
HF (ms²)	372 (208-536)	126 (91-189)	<0,001*
LF/HF ratio	0.600 (0.400-0.898)	2,148 (1.754-2.892)	<0,001*

BMI: Body mass index, HF: High frequency, LF: Low frequency, RMSSD: Square root of the mean squared differences of successive N-N intervals, SDNN: Standard deviation of normal-to-normal (N-N) interval, TP: Total power, VLF: Very low frequency

Table 2: Comparison of HRV characteristics of patients and healthy controls during the postvoiding phase

	OAB Patients (n=41) (postvoiding)	Healthy Controls (n=43) (postvoiding)	P value
Heart rate (beats/min)	75.20 ±9.89	76.65±9,32	0.489
SDNN (ms)	35.29±10.11	44±12.02	0.001*
RMSSD (ms)	30.78±8.72	34.95±7.24	0.019*
TP (ms²)	888.20±215.93	1175.30±301.69	<0,001*
VLF (ms²)	281.15±103.95	323.53±99.60	0.060
LF (ms²)	164 (118.50-211.5)	471 (391-617)	<0.001*
HF (ms²)	427.39±150.66	324.56±115.55	0.001*
LF/HF ratio	0.475±0.262	1.802±0.878	<0,001*

HF: High frequency, LF: Low frequency, RMSSD: Square root of the mean squared differences of successive N-N intervals, SDNN: Standard deviation of normal-to-normal (N-N) interval, TP: Total power, VLF: Very low frequency

Discussion

In the present study, we demonstrated that SDNN, RMSSD (in both prevoiding and post voiding phases) and TP values (in postvoiding phase) were significantly lower in OAB group indicating an attenuation in the HRV. In both prevoiding and postvoiding phases, LF was lower but HF was higher with a resultant significantly lower LF/HF ratio in the OAB group implicating a continuous parasympathetic predominance contrary to the sympathetic predominance observed in healthy controls with a higher LF/HF ratio.

Normally functioning lower urinary tract requires the integration of many regulatory systems including afferent pathways sensing bladder distension and effector pathways modulating storage and voiding phases of urinary bladder. Three types of nervous system are involved in the innervation of lower urinary tract: sympathetic, parasympathetic and somatic nervous system. In storage phase, sympathetic discharge occurs and induces detrusor relaxation together with contraction of the internal urethral sphincter. During voiding, sympathetic activity declines resulting in urethral relaxation and increased parasympathetic discharge contributes to detrusor contraction leading to bladder emptying (19-21). Therefore, it is accepted that any perturbation in ANS may influence and disturb urinary system functions. However, it is difficult to measure autonomic dysfunction in urinary diseases (22).

The reports in the literature that tried to delineate the underlying neurogenic pathophysiology of OAB are limited in number and their patient groups were confined to female gender. Those reports also differ from each other in terms of study designs and results which may even be conflicting. In this regard, the research conducted by Choi-Kim et al. (23) in 2005 showed that the measures of HRV decreased in female patients with OAB. Consequently, Kim-Joo et al. (22) and Im Kim et al. (24) found that both sympathetic and parasympathetic activities were attenuated with a final increase in LF/HF ratio indicating autonomic imbalance with sympathetic predominancy in female patients with OAB. Accordingly, Hsiao-Su et al. (25) demonstrated the presence of higher LF/HF ratio in female patients with OAB while Hubeaux- Deffieux et al. (26) revealed that the predominant type of ANS activity was parasympathetic tone for an empty bladder but it changed to sympathetic tone during artificial bladder filling.

Within this context, Liao & Jaw (8) confirmed the decrease in HRV, however, they intriguingly demonstrated a continuous activity of parasympathetic nervous system before voiding, during voiding and even after the completion of voiding in female patients with OAB. On the contrary, they observed an increased sympathetic activity before voiding, decreased sympathetic and increased parasympathetic activity during voiding and increased sympathetic activity after voiding in the control group comprised of healthy women. Therefore, Liao & Jaw (8) proposed that the disturbance in the order of sympathetic and parasympathetic activities during the storage and voiding phases of urinary system may be the underlying reason of OAB.

Meanwhile, Ben-Dror-Weissmann et al. (27) designed a study in which the sympathetic activity was found lower during the physiologic bladder filling phase in female patients with OAB compared to healthy women. In that study, during bladder filing, sympathetic activity was increased for a short time until the patients with OAB felt a strong desire to void and then decreased to the baseline level. However, in healthy women, the increase in sympathetic activity was observed continuously throughout the whole bladder filling. It is physiologically expected that sustained increase of sympathetic activity during the bladder filling phase is necessary to provide the expansion of urinary bladder. Therefore, this study presumes that alterations toward a decrease in sympathetic activity may be responsible for the feel of urgency in OAB.

Considering the above-mentioned studies, it is reasonable to state that HRV decreases and autonomic balance deteriorates in patients with OAB. However, apparently, it is not possible to conclude that there is a common and convincing hypothesis explaining the exact mechanism leading to OAB. This may be due to the differences in the type of methodology used in these studies. For instance, Choi-Kim et al. (23), Kim-Joo et al. (22), Im-Kim et al. (24) and Hsiao-Su et al. (25) chose to test the HRV with a single measurement at a single point of the time when the bladder was empty or filled with a 100 ml of urine. However, Liao & Jaw (8) and Ben-Dror-Weissmann et al. (27) preferred to test the HRV with sequential measurements at different points in time. Due to the dynamic fashion of the storage and voiding phases of the urinary system, we assume that the research findings of Liao & Jaw (8) and Ben-Dror-Weissmann et al. (27) seem to be more representative of the true voiding patterns of the patients with OAB.

With regard to the study performed by Hubeaux et al., it was seen that HRV was analyzed in two different periods when the bladder was empty and when the bladder was being filled. Nevertheless, we propose that its results may also be confounded as the patients were very limited in number and the bladder was filled artificially. Thereby, we propose that the results of our study provide support for the increased parasympathetic and decreased sympathetic activity resembling the findings of the studies designed by Liao & Jaw (8) and Ben-Dror-Weissmann et al. (27). This similarity may arise from the overlapping methodological approaches between these studies. For instance, all the participants in these studies were instructed to drink certain amount of water and the first measurements were made basing on the sensation of the participants expressing the need to urinate. In addition, OAB was accepted to have a dynamic nature in these studies and separate measurements of HRV were obtained at certain points in time.

Unlike the studies revealing the sympathetic predominance in OAB, we cared in the present study about the participants to be having a feel but not fear of urgency which may interfere with the results of HRV (22-25). Additionally, we did not make measurements during the voiding phase and did not perform invasive procedures in order to prevent an uncomfortable situation that may cause the participants to strain themselves and alter their HRV due to the increase in sympathetic discharge. Therefore, we believe that our study provides more precise estimates of HRV.

From point of pathophysiology, we also suggest that our research results revealing parasympathetic predominance instead of sympathetic activity seem to present a more plausible and convincing explanation that can provide insight into the underlying mechanism of OAB due to the physiological facts about the stimulatory effect of parasympathetic activity on detrusor contraction and bladder emptying (19-21). Therefore, we think that the withdrawal of sympathetic activity and the sustained parasympathetic activity may alter the normal function of storage and voiding phases leading to symptoms of OAB.

There are some limitations in our study. Firstly, the relatively small sample size prevents us to generalize the results to the overall population of patients with OAB. Secondly, we can make assumptions only related with male patients. Thirdly, we did not perform urodynamic studies that could provide more accurate information about detrusor activity, however, it was invasive and not essential. Lastly, the findings cannot be interpreted as whether they are cause or result of OAB.

In conclusion, the OAB in male patients is significantly associated with attenuated HRV parameters and autonomic imbalance towards parasympathetic predominance both in the prevoiding and postvoiding phases. To the best of our knowledge, this is the first study investigating the HRV in male patients with OAB and contributes to the literature by increasing the understanding of ANS function in OAB. Future studies are needed to find a causal relationship and clarify the mechanistic link between ANS and OAB.

Author Contributions

Conception: B.B.K, Data Collection and Processing: B.B.K, A.U.O, Design : B.B.K, Supervision: B.B.K , A.U.O, Analysis and Interpretation: B.B.K, A.U.O , Literature Review: B.B.K, Writer: B.B.K, Critical Review: B.B.K, A.U.O

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