Autonomic Nervous System; Relation Between Prostate Enlargement and LUTS

Otonomik Sinir Sistemi; Prostat Büyümesi ve LUTS Arasındaki İlişki

AÜSS'da Otonomik Sinir Sistemi / Autonomic Nervous System in LUTS

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Özet

Amaç: Alt üriner sistem semptomları ve prostat büyümesi ile otonomik sinir sistemi arasındaki ilişki değerlendirilmek. Gereç ve Yöntem: Alt üriner sistem semptomları olan 67 erkek (57.9±5.6) ve 22 sağlıklı erkek (59.1±5.3) çalışmaya alındı. Holter analizinde sempatik ve parasempatik aktiviteyi temsil eden parametreler gruplar arasında karşılaştırıldı. Her iki grupta prostat hacmi ile otonom sinir sistemi arasındaki ilişki araştırıldı. Bulgular: Alt üriner sistem semptomları olanlarda sempatik sinir sistemi aktivitesinde artış tespit edildi. Ancak bu artış istatistiki anlamlı düzeye ulaşmadı. Her iki grubun prostat hacimleri benzer düzeydeydi. Prostat hacmi sadece alt üriner sistem semptomları olanlarda sempatik sinir sitemi aktivitesi ile ilişkili bulundu. Tartışma: Bilgimiz dahilinde prostat hacmi ile sempatik sinir sitemi arasındaki ilişkinin araştırıldığı çalışmalar prostat hacmi benzer kontrol grubundan yoksundur. Çalışmamızda prostat hacimleri benzer olan iki grup arasında sadece semptomatik grupta prostat hacmi ile sempatik sistem arasında anlamlı ilişki saptandı. Prostat büyümesinde rol alan sempatik sinir sistemi aynı zamanda bu büyümenin semptomatik olup olmayacağını da belirliyor olabilir.

Anahtar Kelimeler

Otonomik Sinir Sistemi; Selim Prostat Hiperplazisi; 24Saat Kalp Hızı; Alt Üriner Sistem Semptomşarı; Sempatik

Abstract

Aim: To evaluate the relationship between autonomic nervous system and LUTS, prostate enlargement. Material and Method: A total of 67 men with LUTS (57.9±5.6years) and 22 healthy men (59.1±5.3years) were enrolled in the study. Parameters of holter influenced by sympathetic and parasympathetic system were compared between patients and controls. Correlation analysis was also done between prostate volume and autonomic system in each group. Results: Parameters of heart rate variability representing sympathetic system were higher in patients with LUTS. However these differences didn't reach statistical significance. Prostate volumes were similar in both groups. Prostate volume was significantly associated with sympathetic system activity in only patients with LUTS. Discussion: To our knowledge in the previous studies the correlation between prostate volume and sympathetic tone was only investigated in patients not in prostate volume matched controls. Although each group has similar prostate volumes, only patients' prostate volumes were significantly correlated with sympathetic tone. The reason for the growth of the prostate may also determine whether the growth will be symptomatic or not.

Keywords

Autonomic Nervous System; Benign Prostate Hyperplasia; 24Hour Heart Rate Variability; Lower Urinary Tract Symptoms; Sympathetic

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Introduction

It is common for men to have prostate enlargement without having lower urinary tract symptoms (LUTS) and vice versa. The exact etiopathogenesis of benign prostate hyperplasia (BPH) and "LUTS in BPH" remain ambiguous. There is increasing evidence that sympathetic overactivity appear to have an important role in the pathogenesis of the BPH [1,2]. Sympathetic nerve system overactivity was also shown in patients with LUTS suggestive of BPH [3,4].

Extraprostatic factors acting on prostate with underlying anatomical and/or physiological derangements may lead to the emergence of symptomatic manifestations of BPH. Further understanding of these extraprostatic factors is mandatory. Factor or factors those involved in prostate enlargement; may also lead to development of LUTS in subsequent years.

Heart rate variability (HRV) is being used widely to assess global sympathetic and parasympathetic activity [5,6]. We organized a study to evaluate the autonomic nervous system (ANS) status ¬using 24hours HRV recordings in patients with LUTS suggestive of BPH and healthy age and prostate volume matched controls to reveal any etiologic association between LUTS and prostate enlargement.

Material and Method

A total of 89 men, 67 with LUTS and 22 healthy controls were enrolled in the study. Ethic committee approval was taken and informed consent was obtained by all participants.

The patients' medical history was obtained, and physical examination, including digital rectal examination and urinalysis, were performed. The inclusion criteria were, prostate volume larger than 20cc and peak urinary flow lower than 15ml/second, IPSS>7 [7]. Control subjects were chosen from men applied to urology clinic for routine checkup. None of the control subjects had any kind of LUTS.

Our exclusion criteria were as follows: previous medical or surgical intervention for BPH or prostate cancer, anticholinergic or cholinergic, sympathomimetic or sympatholytic medication within 1 month of the entry of the study, treatment with any medication which can affect testosterone or estrogen, presence of any renal or hepatic impairment, and abnormally lower or higher tiroid stimulating hormone levels, serum prostate specific antigen (PSA)>3 ng/mL, urinary incontinence, history of any type of malignancy, cardiovascular disease, hypertension, cerebrovascular accident, diabetes mellitus, any known primary neurological conditions, such as multiple sclerosis or Parkinson's disease, or other neurological diseases known to affect bladder function, and active urinary tract infection.

Patients wear the Holter monitor while carrying out their usual daily activities for 24 hours. ECG electrodes were placed on the precordial area. Holter monitoring was performed by use of a digital Holter monitor (DMS 300-7, Compact Flash Card Holter Recorder, DMS, Nevada, USA). The data stored were processed by use of the Cardio Scan 8.0 software to assess HRV. Duration and frequency of HRV were assessed.

In a continuous ECG record, each QRS complex resulting from sinus node depolarizations is called normal-to-normal intervals (iNN). Assessment of HRV in the time domain based on iNN. The following parameters were derived by use of statistical methods mean of the standard deviations of iNN every five minutes (SDNN); root of the mean squared difference of successive iNNs (RMSSD).

When assessing HRV in the frequency domain, total power (TP) a low frequency (LF) band (between 0.04 and 0.15 Hz), very low frequency (VLF) band (between 0.003-0.04 Hz) and a high frequency (HF) band (between 0.15 and 0.40 Hz) were used. The LF/HF ratio was obtained.

Age, height, body mass index (BMI), PSA, SDNN, VLF and RMSSD were compared between patients and controls using an independent sample t test. Weight, prostate volume, LF, power, mean heart rate, HF and LF/HF ratio were compared with Mann–Whitney U test due to non-normal distribution of these parameters in the groups. Relation between prostate volume and holter parameters were assessed by pearson correlation analysis. Statistical calculations were performed using PASW version 18. The null hypothesis was rejected if p was <0.05.

Results

There was no statistically significant difference between the LUTS and the control group; regarding age, height, weight, BMI, prostate volume and PSA values.(Table 1)

Table 1. Clinical data, prostate volume and PSA values of control and LUTS groups.

	Control	LUTS	p
Age	59.1±5.3	57.9±5.6	0.396
Height (m)	1.68±0.1	1.70±0.1	0.139
Weight (kg)	81.8±10.9	80.0±14.2	0.275
BMI	28.8±3.7	27.3±4.2	0.175
Prostate volume (cc)	48.4±19.8	50.7±20.5	0.644
PSA (ng/mL)	1.5±0.8	1.8±1.1	0.355

BMI: Body mass index

The SDNN and heart rate was lower in LUTS group; power, LF and LF/HF ratio was higher in patients with LUTS than control subjects. However these differences didn't reach statistical significance.(Table 2)

Table 2: HRV parameters of control and LUTS groups.

		Control	LUTS	p
SYMPATHETIC	SDNN(ms)	127.2±29.3	125.4±27.7	0.792
	LF(ms2)	446.5±337.4	539.6±269.3	0.191
	VLF(ms2)	1688.7±832.8	2004.6±747.9	0.098
	TP(ms2)	2255.8±1055.3	2515.8±829.8	0.238
	HR	73.1±5.4	72.1±5.1	0.465
PARASYMPATHETIC	RMSSD(ms)	25.1±4.1	23±4.6	0.067
	HF(ms2)	108.9±61.1	128.5±69.1	0.239
BALANCE	LF/HF	3.9±1.4	4.5±2	0.224

Prostate volume was significantly correlated with SDNN and heart rate in only patients with LUTS. (Table 3)

Discussion

Since lower urinary tract is mainly controlled through sympathetic and parasympathetic nervous systems, ANS is believed to be one of the etiologic factors in LUTS [3,4]. There are also

Table 3. Correlations between HRV parameters and prostate volume in control and LUTS groups.

		PROSTATE (CONTROL)		PROSTATE (LUTS)	
		r	p	r	p
SYMPATHETIC	SDNN(ms)	-0.011	0.960	0.255*	0.037
	LF(ms2)	-0.155	0.491	0.125	0.313
	VLF(ms2)	0.209	0.352	0.173	0.161
	TP(ms2)	-0.282	0.203	0.209	0.090
	HR	0.198	0.378	0.346**	0.004
PARASYMPATHETIC	RMSSD(ms)	0.312	0.158	-0.078	0.532
	HF(ms2)	0.289	0.191	-0.035	0.779
BALANCE	LF/HF	0.238	0.286	0.013	0.918

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

findings suggesting that sympathetic stimulation may promote prostatic hyperplasia [2,8]. However to our knowledge none of these studies assess these two parameters' (LUTS and prostate enlargement) association with ANS in their patient and control groups simultaneously. For instance McVary et al found significant correlation between prostate volume, IPSS and autonomic variables, but the study lacks a control group [3]. Choi et al assessed the HRV parameters in patients with LUTS and control subjects, but they didn't evaluate prostate volume in their study [4]. Sandfeldt and Hahn showed significant relation between prostate volume and HRV parameter but this study also lacks a control group [9]. We found significant correlation between sympathetic tonus and prostate volume in patients with LUTS. Although control group's prostate volume was not statistically different from patients; there was no correlation between prostate volume ANS status in control subjects.

Cardiac muscle has an inherent ability to beat but the nodal system plays a critical role in cardiac automaticity. However the HRV and rhythm are largely under the control of the ANS. The degree of HRV depends on the influence of sympathetic and parasympathetic activity on the sinus node, and variation and variability reflect spontaneous changes in autonomic activity [10]. Since, HRV is a new and important tool for studying autonomic control of the heart and ANS function we used HRV parameters to compare the status of ANS between men with LUTS and healthy controls.

Parameters of HRV influenced by ANS have been assessed. Most investigators have suggested that HF and RMSSD are predominantly a response to changes in the parasympathetic tone, whereas LF, TP and SDNN are influenced by adrenergic activities. In other words a rise in parasympathetic activity will result in increase HF and RMSSD, rise in sympathetic activity will result increase in LF and SDNN. The LF/HF ratio reflects the balance between the two components of the ANS [11,12]. However, VLF constitutes most of the TP in the HRV. VLF power in part reflects thermoregulatory mechanisms, fluctuation in activity of the renin-angiotensin system, and the function of peripheral chemoreceptors [13]. VLF may thus reflect not only cardiac stress but also general systemic stress [14].

Choi et al. found that men with LUTS had sympathetic overactivity compared to controls, and also they detected that the mean LF/HF ratio of voiding symptom- predominant group was higher than storage symptom–predominant group [4]. McVary et al. found significant associations between LUTS, prostate volume and elevated urinary catecholamines, blood pressures, heart rate after tilt-table testing [8]. Ullrich et al. also found significant associations between increases in diastolic blood pressure, serum cortisol levels and prostate enlargement and LUTS following a laboratory stress test [15]. We also found VLF, LF, LF/HF and HR increased (sympathetic activity) in patients with LUTS than controls. However this increase didn't reach statistical significance.

The ranges of HRV values vary in patients with LUTS and even in healthy subjects in our study. Other authors also noted high ranges in their studies just like we did. [4,10-14]. To minimize the range, number of the subjects in control and study groups should be kept more crowded in such studies.

Subjects in our study were slightly younger than the patients with anticipated LUTS symptoms. Diseases such as diabetes and hypertension were excluded in order to avoid their possible effects on ANS. These exclusion criteria might be responsible for our younger study population.

Prostate enlargement may consequence from sympathetic activity [2,8,16] and there is also studies showing higher sympathetic tone in patients with large prostates [3,9]. There are so many asymptomatic men with enlarged prostates. In order to reveal the status of ANS in asymptomatic man with prostate enlargement we also evaluated prostate volume matched control subjects in the present study. We found significant correlation between prostate volume and SDNN and HR which represents sympathetic tone in patients with LUTS. In control group there was no significant correlation. While prostate enlargement in patients with LUTS may be due to sympathetic tone, it may be due to other etiologies rather than ANS imbalance in patients without LUTS.

In this preliminary study we couldn't reach a statistical significance between men with and without LUTS in HRV parameters. We found significant correlation between prostate volume and sympathetic activity in symptomatic patients as other studies. However in addition to other studies we also investigated the correlation between prostate volume and ANS in prostate and age matched asymptomatic controls and we didn't find significant correlation in control group.

Hormones, stromal-epithelial interactions, growth factors, neurotransmitters, cytokines, sympathetic overactivity may play a role, either singly or in combination, in the etiology of the hyperplastic process. In which man LUTS will accompany this hyperplastic process? Answer to this question may be lying in the answer of which factor predominated the hyperplastic process of prostate?

Competing interests

The authors declare that they have no competing interests.

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