ORIGINAL ARTICLE

Assessment of cardiac autonomic functions by heart rate variability in patients with restless leg syndrome

Huzursuz bacak sendromlu hastalarda kalp otonom fonksiyonlarının kalp hızı değişkenliği ile incelenmesi

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ABSTRACT

Objective: The aim of the present study was to investigate cardiac autonomic effects in restless leg syndrome (RLS) using heart rate variability (HRV).

Methods: A total of 35 patients with RLS and 35 healthy individuals were enrolled in the study. The severity of RLS symptoms was assessed using the International Restless Legs Syndrome Study Group rating scale (IRLS). The correlation between the severity of RLS symptoms and HRV parameters measured on an electrocardiogram was analyzed.

Results: There were no statistically significant differences between the 2 groups with respect to age, gender, or body mass index. The mean heart rate was 85±7.1 bpm in the RLS group compared with 79.6±5.5 bpm in the control group (p=0.001). The standard deviation (SD) of all normal to normal (NN) intervals (SDNN), the mean of the deviation of 5-minute NN intervals over the entire recording (SDNN index), and the SD of the average NN intervals calculated over a 5-minute period of the entire recording (SDANN) were significantly lower in the RLS group compared with the control group (p<0.05 for all). There were no statistically significant differences between the 2 groups in the square root of the mean squared differences of successive NN intervals (RMSSD) and the proportion of adjacent RR intervals differing by >50 milliseconds in the 24-hour recording (pNN50) values (p=0.119 and p=0.07, respectively). In patients with RLS, the low frequency (LF) power and LF/high frequency (HF) ratio were significantly higher than those in the control group (2248.6±245.6 *vs* 712.1±346.3, 10.7±3.7 *vs* 2.9±1.8; p<0.0001 and p<0.0001, respectively). Compared with the control group, the RLS group had lower values for HF power, but the difference was not statistically significant (p=0.07). The severity of RLS symptoms was negatively correlated with the SDNN, SDANN index, and pNN50 (r=-0.453 and p=0.009, r=-0.340 and p=0.046, r=-0.446 and p=0.007, respectively), and positively correlated with LF power (r=0.681 and p<0.0001).

Conclusion: The study data demonstrated that cardiac autonomic impairment is associated with RLS.

ÖZET

Amaç: Bu çalışmada huzursuz bacak sendromlu (HBS) hastalarda kalp hızı değişkenliğini (KHD) inceleyerek kalp otonom fonksiyonlarını araştırmayı amaçladık.

Yöntemler: HBS tanısı konulan 35 hasta ve benzer özelliklere sahip 35 sağlıklı birey çalışmaya alındı. HBS semptomlarının şiddeti Uluslararası Huzursuz Bacak Çalışma Grubu Şiddeti Ölçeği kullanılarak değerlendirildi. HBS semptom şiddeti ve KHD parametreleri arasındaki ilişki değerlendirildi.

Bulgular: Yaş, cinsiyet veya vücut kitle indeksi açısından iki grup arasında istatistiksel açıdan anlamlı farklılıklar yoktu. HBS grubunda ortalama kalp atım hızı 85±7.1 /dk iken kontrol grubunda 79.6±5.5 /dk idi (p=0.001). Kontrol grubuna göre tüm normal değerler arası aralıkların (NN) standart sapması (SSNN), tüm kayıt süresince hesaplanmış 5-dakikalık NN aralıklarının ortalama sapması (SSNN indeksi) ve yine tüm kayıt süresince bir 5-dakikalık zaman diliminde ortalama NN aralıklarının hesaplanmış SS'si (SSANN) HBS grubunda anlamlı derecede daha düşüktü (tümü için p<0.05). İki grup arasında ardışık NN aralıklarının ortalama kare farklılıklarının kare kökü (RMSSD) ve 24 saatlik kayıt boyunca 50 milisaniyeden daha uzun süre fark eden bitişik RR aralıklarının oranı (pNN50) açısından fark yoktu (sırasıyla, p=0.119 ve p=0.07). HBS hastalarında düşük frekans (DF)/yüksek frekans (YF) oranı kontrol grubuna göre anlamlı derecede daha yüksek idi (sırasıyla, 2248.6±245.6 ve 712.1±346.3, 10.7±3.7 ve 2.9±1.8; p<0.0001 ve p<0.0001). Kontrol grubuyla karşılaştırıldığında HBS grubunda DF güç değerleri daha düşük olmasına rağmen farklılık istatistiksel açıdan anlamlı değildi (p=0.07). HBS semptomlarının şiddet derecesi SDNNN, SDANN indeksi ve pNN50 ile negatif (sırasıyla, r=-0.453 ve p=0.009, r=-0.340 ve p=0.046, r=-0.446 ve p=0.007) ve YF ile pozitif bir korelasyon göstermekteydi (r=0.681 ve p<0.0001).

Sonuç: Çalışma verileri kardiyak otonomik bozukluğun HBS ile ilişkili olduğunu göstermiştir.

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Restless leg syndrome (RLS) was first described by Sir Thomas Willis in 1672.[1] Swedish neurologist Ekbom systematically described the disorder and named it RLS in 1945.[2] It is a common condition, consisting of a strong urge to move the legs that occurs during inactivity and at night. It causes sleep disturbance and has a negative impact on quality of life. The pathophysiology of RLS is largely unknown. Abnormalities of the dopaminergic system have been suggested as a possible etiology.[3] The prevalence of RLS has been reported to be between 5% and 10%.[4] Symptoms are most common in lower limbs, but may also involve the arms or other parts of the body.[5–7]

Patients with RLS have significantly more autonomic complaints than the general population, such as sialorrhea, constipation, early abdominal fullness, lightheadedness when standing, and heat intolerance.[8] Additionally, significant elevations in nocturnal blood pressure and pulse rate, and an increased prevalence and incidence of hypertension, cardiovascular disease, and cerebrovascular disease suggestive of autonomic dysfunction have been found in RLS patients.[9] Although several epidemiological studies have demonstrated an increased risk for cardiovascular disease in RLS,[10,11] relatively few studies have investigated the underlying mechanisms involved in cardiovascular disease.

Heart rate variability (HRV) reliably reflects cardiac autonomic balance and indirectly measures sinoatrial node functions.[12] It is known that a decrease in HRV is the earliest sign of cardiac autonomic neuropathy.[12–14] The present study was carried out (1) to investigate cardiac autonomic function by assessing HRV in patients with RLS and (2) to determine if there was a correlation between RLS symptoms and cardiac autonomic dysfunction in these patients.

METHODS

Thirty-five patients with RLS and 35 age- and gender-matched healthy individuals were enrolled in the study. Patients with RLS who were followed up at our neurology clinic were enrolled in the study. The diagnosis of RLS was made on the basis of clinical symptoms using the revised International Restless Legs Syndrome Study Group (IRLSSG) criteria published in 2012.[15]

The severity of RLS symptoms was assessed by using the IRLSSG rating scale (IRLS) summed score levels of mild (0–10), moderate (11–20), severe (21–30) and very severe (31–40).[16]

Abbreviations:

BMI	*Body mass index*
HF	*High frequency*
HRV	*Heart rate variability*
LF	*Low frequency*
NN	*Normal to normal interval*
pNN50	*Proportion of adjacent RR intervals differing by >50 ms in a 24-hour recording*
RLS	*Restless leg syndrome*
RMSSD	*Square root of the mean squared differences of successive NN intervals*
SD	*Standard deviation*
SDANN	*SD of the average NN intervals calculated over a 5-minute period of the entire recording*
SDNN	*SD of all NN intervals*

Patients who had been receiving treatment for RLS and who had received prescriptions for antidepressants, antiarrhythmic drugs, beta-blockers, calcium channel blockers, or with a history of valve disease or replacement, pacemaker implantation, atrial fibrillation, arrhythmias, thyroid disease, diabetes mellitus, hypertension, chronic renal failure, liver disease, ischemic heart disease, sleep apnea syndrome, congestive heart failure, stroke, or neurological disorder were excluded from the study. The study was approved by the ethics committee and was performed according to the Declaration of Helsinki. Written informed consent was obtained from all of the patients.

Twenty-four hour Holter electrocardiogram recordings were obtained using 3-channel digital recorders (Cardioscan Premier Version 12; DM Systems Co., Ltd. Beijing, China). Recordings lasting more than 22 hours and of sufficient quality for evaluation were included in the analysis. HRV was measured using the algorithms of the commercial device. Time domain HRV indices were analyzed with a statistical method in which the square root of the mean squared differences of successive normal to normal (NN) intervals (RMSSD), the standard deviation (SD) of all NN intervals (SDNN), the mean of the deviation of the 5-minute NN intervals over the entire recording (SDNN index), the SD of the average NN intervals calculated over a 5-minute period of the entire recording (SDANN), and the proportion of adjacent RR intervals differing by >50 milliseconds in the 24-hour recording (pNN50) were measured. Spectral analysis of HRV included total power, which represents the variability of the entire signal and was obtained by summing the powers of each frequency band, a high frequency (HF) component (0.15–0.40 Hz), and a low frequency (LF) component (0.04–0.15 Hz). The LF/HF power was calculated for all of the participants. Sympathetic and parasympathetic activities were au-

tomatically calculated through an analysis program. All of the measurements were performed according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[12]

Statistical analysis

Continuous variables were expressed as mean±SD, and categorical variables were expressed as percentages. Statistical analyses were performed by using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The mean values for the RLS patients and the controls were compared using the 2-sample t-test. The correlations between the observed variables were examined with Pearson's correlation test. A p value <0.05 was considered statistically significant.

RESULTS

Table 1 illustrates the clinical characteristics of the study groups. There were no statistically significant differences between the 2 groups with respect to age, gender, body mass index (BMI), smoking, blood pressure, ejection fraction, levels of fasting blood glucose, creatinine, hemoglobin, or thyroid-stimulating hormone.

The mean heart rate was 85±7.1 bpm in the RLS group compared with 79.6±5.5 bpm in the control group (p=0.001). The SDNN, SDANN, and SDNN index were significantly lower in the RLS group compared with the control group (p<0.05 for all). Likewise, the RMSSD and the pNN50 decreased in the patient group, but not to a statistically significant degree (p=0.119 and 0.07 respectively). In patients with RLS, the LF power and the LF/HF ratio were significantly higher than those in the control group (2248.6±245.6 *vs*. 712.1±346.3, 10.7±3.7 *vs*. 2.9±1.8; p<0.0001 and p<0.0001 respectively). Compared with the control group, the RLS group had lower HF power values, but the difference was not statistically significant (p=0.07). The HRV parameters of the patients are shown in Table 2.

The RLS group was found to have greater sympathetic activity and decreased parasympathetic activity compared with the control group (95.04%±1.2 vs 91.1%±4.02, 4.9%±1.2 *vs*. 8.8%±4.0; p<0.0001 for both). The ratio of sympathetic and parasympathetic activity was significantly greater in the patient group compared with the control group (20.1±4.4 and 13.3±7.6; p<0.0001).

The severity of RLS symptoms was negatively correlated with the SDNN, SDANN index, and pNN50 (r=-0.453 and p=0.009, r=-0.340 and p=0.046, r=-0.446 and p=0.007, respectively) and positively correlated with LF power (r=0.681 and p<0.0001). Table 3 shows the correlations between the IRLS summed score and HRV parameters.

Table 1. Clinical characteristics of the patients

	Restless leg syndrome (n=35)	Control (n=35)	*p*
Age (years)	41.9±8.8	43.3±9.9	0.527
Gender (female), n (%)	19 (54.2)	18 (51.4)	0.892
Smoking, n (%)	15 (42.8)	14 (40)	0.894
Systolic blood pressure (mm Hg)	132.4±14.5	128.5±16.4	0.252
Diastolic blood pressure (mm Hg)	85.4±6.4	81.9±7.5	0.158
Body mass index (kg/m²)	28.7±3.4	27.3±4.1	0.875
Fasting blood glucose (mg/dL)	101±11	97±13	0.411
Creatinine (mg/dL)	0.86±0.11	0.83±0.12	0.365
Ejection fraction (%)	65±9	63±7	0.455
Hemoglobin (g/dL)	12.1	13.1	0.09
Thyroid-stimulating hormone (μIU/mL)	1.71±0.85	1.81±0.9	0.49
Heart rate	85±7.1	79.6±5.5	0.001
Recording time (hours)	23.1±1.1	23.3±1.2	0.97

Table 2. Heart rate variability parameters of the patients

	Restless leg syndrome group	Control group	*p*
SDNN (ms)	133.7±20.1	144.8±23.9	0.04
SDANN (ms)	119.1±18.9	132.9±23.7	0.009
SDNN index (ms)	52±10.5	57.4±10.8	0.03
RMSSD (ms)	28.2±7.2	31.4±9.4	0.119
pNN50 (%)	7.9±1.9	9.8±5.4	0.07
Low frequency	2248.6±245.6	712.1±346.3	<0.0001
High frequency	229.0±68.8	278.2±144.8	0.07
Low frequency/High frequency	10.7±3.7	2.9±1.8	<0.0001
Sympathetic activity (%)	95.04±1.2	91.1±4.02	<0.0001
Parasympathetic activity (%)	4.9±1.2	8.8±4.0	<0.0001
Ratio S/P	20.1±4.4	13.3±7.6	<0.0001

pNN50: The proportion of adjacent RR intervals differing by >50 ms in the 24-hour recording; RMSSD: The square root of the mean squared differences of successive normal to normal intervals; SDANN: The standard deviation of the average normal to normal intervals calculated over a 5-minute period of the entire recording; SDNN: The standard deviation of all normal to normal intervals; SDNN index: The mean of the deviation of the 5-minute normal to normal intervals over the entire electrocardiogram recording.

DISCUSSION

We investigated cardiac autonomic functions with regard to RLS and examined whether there existed an underlying cardiac autonomic dysfunction. In our study, we evaluated HRV metrics in time and frequency domain analysis in patients with RLS and without coexisting diseases. The study data indicated that cardiac autonomic impairment was associated with RLS. The time domain markers of SDNN, SDANN, and SDNN index were found to be significantly lower in patients with RLS, which might reflect a predominant sympathetic stimulation of the heart. Compared with the controls, the RLS patients had a significantly greater LF power value and LF/HF ratio, which indicated elevated sympathetic nerve activity. It appeared that parasympathetic function was less compromised in RLS patients; the RMSSD, pNN50, and HF power, which reflect parasympathetic activity, were not significantly different between the 2 groups. Perhaps the most important distinguishing feature of the present study is the relationship between cardiac autonomic dysfunction and the severity of RLS symptoms.

Table 3. Correlations between IRLS summed score and HRV parameters

	r	p
SDNN (ms)	-0.453	0.009
SDANN (ms)	-0.340	0.046
pNN50 (%)	-0.446	0.007
Low frequency	0.681	<0.0001
High frequency	0.294	0.08

HRV: Heart rate variability; IRLS: International Restless Legs Syndrome Study Group rating scale; pNN50: The proportion of adjacent RR intervals differing by >50 ms in the 24-hour recording; SDANN: The standard deviation of the average normal to normal intervals calculated over a 5-minute period of the entire electrocardiogram recording; SDNN: The standard deviation of all normal to normal intervals.

HRV is a measure of continuous interplay between sympathetic and parasympathetic influences on heart rate. A high HRV is associated with good cardiovascular health and indicates a healthy heart that quickly responds to internal or external changes in a highly adaptive way. Several studies have demonstrated that a low HRV is associated with increased cardiovascular morbidity and mortality in both healthy individuals and those with coronary artery disease.[17,18] There are 2 different methods of HRV analysis: time domain and frequency domain analysis. In time domain analysis, the SDNN, SDANN, and SDNN index reflect overall variability, and the RMSSD and pNN50 estimate predominantly parasympathetic modulation. In frequency domain analysis, vagal tone is considered a major contributor to the HF component, and LF is believed to reflect both sympathetic and parasympathetic influences. Sympathovagal balance is frequently described using the LF/HF ratio.

The pathophysiology of RLS is unclear. The leading hypothesis for its pathogenesis is via a dopaminergic pathway, which suggests that there is a dopaminergic deficit in RLS. There are 4 main dopamine pathways in the brain: striatonigral, mesolimbic, mesocortical, and tuberoinfundibular. Dopaminergic neurons that originate in the cell group of A11 of the hypothalamus travel within the diencephalospinal dopaminergic pathway and innervate the lumbosacral cord, which modulates sensory and motor processes. Decreased activity of the A11 neuronal group causes increased sympathetic outflow to the periphery, changes the sensory information returned to the spinal cord, and results in paraesthesia perceived at the cortical level.[19] It has been demonstrated that stereotaxic bilateral 6-hydroxydopamine lesions into the A11 nucleus in rats resulted in behaviors consistent with RLS.[20] In addition, there is a well-known association between iron deficiency and RLS. Iron is an essential co-factor for tyrosine hydroxylase, which is rate-limiting enzyme in the synthesis of dopamine. Furthermore, D2 receptors contain iron atoms, which could explain why some RLS patients find relief with iron supplements.[21]

Several lines of evidence suggest that patients with RLS have autonomic system abnormalities. Symptoms related to the autonomic nervous system have been more frequently reported in patients with RLS.[8] It has been shown that men with RLS had higher rates of erectile dysfunction.[22] Autonomic responses to the head-up tilt test are blunted in patients with RLS during wakefulness.[23] There is also an increased prevalence of hypertension in patients with RLS, which is suggestive of autonomic dysfunction.[24]

The findings of our study were consistent with other studies that have reported cardiac autonomic dysfunction in RLS patients. Cikrikcioglu et al.[25] reported a higher erythrocyte sedimentation rate and mean platelet volume in RLS patients than in controls. They noted low HRV triangular index values, indicating elevated sympathetic myocardial activity. Bertisch et al.[26] studied 20 RLS patients without cardiovascular disease and 20 matched controls. The patients with RLS had a lower baroreflex gain, lower leg blood flow, and greater leg vascular resistance. As other indices of cardiovagal control, including respiratory sinus arrhythmia and Valsalva ratios, did not differ between the groups, they concluded that RLS patients had compromised cardiovagal control, specific to the arterial baroreflex, potentially due to heightened sympathetic flow. The meaningful difference with our study was the existence of a relationship between the severity of RLS and HRV measures. The IRLS summed score was significantly correlated with LF power and negatively correlated with the SDNN, SDANN index, and pNN50. These findings suggested that the level of cardiac autonomic dysfunction was higher in more severely affected patients. During the study period, pharmacological treatment potentially affecting HRV was avoided and the patients were free of medication effects during ambulatory electrocardiogram monitoring.

An increase in sympathetic activity leads to an increase in heart rate as well as blood pressure, and is associated with increased cardiovascular morbidity and mortality. Sympathetic hyperactivity has been shown to contribute to endothelial damage and atherosclerosis. Sympathetic nerve hyperactivity may trigger ventricular arrhythmias.[27]

Decreased HRV is a risk factor for cardiovascular morbidity and mortality; therefore, the results of our study could be of importance to clinical practice.[28] Our research indicates that there is a relationship between RLS and increased sympathetic cardiac modulation. An adverse cardiovascular risk factor profile and increased activity of the sympathetic nervous system may contribute to an increased cardiovascular disease risk in patients with RLS.

Study limitations

This was a retrospective analysis of data at a single center and the number of patients was small. Polysomnography was not used as a diagnostic tool. We assessed self-reported measures of sleep duration and quality, and therefore did not account for potential differences in objectively measured sleep. Follow-up assessments were not conducted and the results might not predict long-term outcomes.

Conclusion

RLS is a neurological disorder that is associated with autonomic nervous system abnormalities. A decreased SDNN, SDANN, and SDNN index, and an increased LF power and LF/HF ratio may be the early signs of cardiac autonomic dysfunction in patients with RLS.

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