Correlations between autonomic dysfunction and circadian changes and arrhythmia prevalence in women with fibromyalgia syndrome

Fibromyalji sendromu saptanan kadın hastalarda otonomik fonksiyon bozuklukları ve günlük otonomik değişimler ile aritmi sıklığı arasındaki bağıntılar

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ABSTRACT

Objective: It is known that increased sympathetic activity and decreased parasympathetic activity are present in patients with fibromyalgia syndrome (FMS). This study aims to investigate the correlations of autonomic dysfunction and differences in autonomic circadian activity with arrhythmia prevalence in women with FMS.

Methods: Fifty female patients with FMS and 30 healthy female controls were included in this cross-sectional, case-controlled study. A 12-lead electrocardiogram and 24-hour Holter monitoring were performed in all patients to evaluate arrhythmias and autonomic function tests. Heart rate variability (HRV) parameters were utilized to detect autonomic dysfunction in patients with FMS. HRV measurements were performed in total 24-hour, day time (06:00-22:59), night time (23:00-05:59) periods and during autonomic tests (stand - supine, inspiration-expiration and Valsalva tests) using 24-hour Holter monitoring recordings. Student t-test , Mann–Whitney U and Pearson Chi-square tests were used for comparisons of the data between groups. The correlation of data was tested by using Spearman correlation analysis.

Results: The mean ages of the patient and control groups were 38±7.4 and 36±8.1 years, respectively. In HRV measurements, high frequency (HF) power, was significantly decreased in the patient group as compared with control group (167.4 $msec^2$ (107.0- 312.0) vs.314.5 $msec^2$ (124.0- 905.0), p=0.017). The low frequency/HF ratio (LF/HF) values for total 24 hours (2.22±0.18 vs. 1.22±0.12, p<0.001) and in the night time period (2.78±1.97 vs.1.15±0.77, p<0.001) were found to be significantly higher in the patient group than in control one. The ratio of LF/HF_{Day} / LF/HF_{Night} was markedly higher in the control group (2.67 (1.22- 5.65) vs. 1.45 (0.83- 2.05), p=0.004). The prevalence (p=0.028) and total number (127.1±21.4 vs. 187.3±62.3, p=0.019) of supraventricular extrasystoles in 24-hour period was higher in the patient group .

Conclusion: The sympathetic activity was significantly increased and parasympathetic activity significantly decreased in FMS patients. Additionally, significant autonomic circadian activity changes were also detected in these patients. These autonomic changes might be linked to increased arrhythmia prevalence. *(Anadolu Kardiyol Derg 2009; 9: 110-7)*

Key words: Fibromyalgia, autonomic nervous system, heart rate variability, electrocardiography, arrhythmia

ÖZET

Amaç: Fibromiyalji sendromu (FMS) bulunan hastalarda artmış sempatik ve azalmış parasempatik aktivitenin varlığı bilinmektedir. Bu çalışma FMS bulunan kadın hastalarda otonomik disfonksiyon ve günlük otonomik aktivite değişimleri ile aritmi sıklığının araştırılmasını amaçlamaktadır.

Yöntemler: Elli FMS bulunan ve 30 sağlıklı kadın (kontrol) enine-kesitli ve vaka kontrollü bu çalışmaya alındı. Her hastaya, otonom sınır sistemi ve aritmi analizi amacı ile 12 kanallı elektrokardiyografi ve 24 saatlik Holter takibi yapıldı. Kalp atım hızı değişkenliği parametreleri 24 saat, gündüz (06:00-22:59) ve gece (23:00-05-59) ve yapılan otonomik testlere (ayağa kalkış ve yatış, nefes alma ve verme ve Valsalva testleri) ait zaman aralıklarında 24 saat Holter takip kayıtları kullanılarak ölçüldü. İstatistiksel değerlendirmede verilerin karşılaştırılmasında Student t, Mann-Whitney U ve Pearson Ki-kare testleri kullanıldı. Veriler arasındaki korelasyonun tespiti için Spearman korelasyon analizi kullanıldı.

Bulgular: Hasta ve kontrol gruplarının ortalama yaşları sırasıyla 38±7.4 ve 36±8.1 idi. Kalp atım hızı değişkenliği ölçümlerinde yüksek frekans (YF) kuvveti hasta grubunda önemli ölçüde düşük olarak bulundu [167.4 msn^2 (107.0- 312.0) karşı 314.5 msn^2 (124.0- 905.0), p=0.017). Düşük frekans (DF) / YF oranı (DF/YF) 24 saatlik dönem için (2.22±0.18'e karşı 1.22±0.12, p<0.001) ve gece dönemi için (2.78±1.97'ye karşı 1.15±0.77, p<0.001) hasta grubunda artmış bulundu. Gündüz ve gece arasında otonomik değişimi yansıtan $DF/YF_{Gündüz}$ / DF/YF_{Gece} oranı kontrol grubunda daha yüksek olarak bulundu (2.67 (1.22-5.65) karşı 1.45 (0.83- 2.05), p=0.004). Supraventriküler ekstrasistollerin sıklığı (p=0.028) ve toplam günlük sayısı (127.1±21.4'e karşı 187.3±62.3, p=0.019) FMS grubunda daha fazla idi.

Sonuç: Fibromiyalji sendromu saptanan hastalarda sempatik aktivite artmış; parasempatik aktivite azalmıştır. Ayrıca bu hastalarda günlük otonomik aktivite değişiminde önemli farklılıklar mevcuttur. Otonomik değişikler artmış aritmi sıklığı ile bağlantılı olabilir. *(Anadolu Kardiyol Derg 2009; 9: 110-7)*

Anahtar kelimeler: Fibromiyalji, otonomik sinir sistemi, kalp atım hızı değişkenliği, elektrokardiyografi, aritmi

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Introduction

Fibromyalgia syndrome (FMS) is an idiopathic, chronic syndrome of nonarticular-muscular origin and is characterized by widespread and well-localized anatomic points that are painful spontaneously especially during palpation (1). Its prevalence is about 2% in the general population (2). Pathophysiological mechanisms of FMS include multiple factors that interact to amplify pain. The primary problem is currently believed to be heterogeneous neuroendocrine dysfunction, leading to central sensitization or sensitivity. Neuroendocrine dysfunction also includes autonomic dysfunction simultaneously (3). Furthermore, some authors suggested that some of the signs and symptoms of FMS may be due to autonomic dysfunction (2, 4). Increased sympathetic and decreased parasympathetic activities were detected in FMS patients in several previous studies. In most studies, the results of a 24-hour period were used for indirect evaluation of autonomic activity (2, 4, 5). Data in the literature about circadian autonomic changes in FMS are limited. It is well known that circadian autonomic changes are important for the mechanisms of many other pathologic conditions (6-8). Moreover, pathologic changes in sympathetic and parasympathetic activity can cause some types of arrhythmias (9). To our knowledge, there is no study in the literature documenting the arrhythmia prevalence in FMS.

In this study, we aimed to investigate autonomic dysfunction by using various autonomic tests and to investigate related daytime and nighttime autonomic changes in patients with FMS by means of heart rate variability (HRV) analysis. We also searched the arrhythmia prevalence in our patient group and their correlation with autonomic activities.

Methods

Fifty female patients admitted to the Physical Medicine and Rehabilitation (PMR) outpatient clinic with widespread musculoskeletal pain and diagnosed as primary FMS according to the American College of Rheumatology criteria (10) and 30 healthy age-matched females as controls were included in this cross-sectional case-controlled study. Only female patients were included in the study in order to avoid the probable effects of autonomic differences between genders. The study was approved by the Local Ethical Committee. The patients were informed about the study and all provided signed informed consents.

Patient selection

Exclusion criteria

Patients with congenital heart disease, cardiomyopathies (dilated, hypertrophic or restrictive), left ventricular hypertrophy, heart failure (ejection fraction [EF] <50%), conduction disturbances (except first-degree atrioventricular [AV] block), hypertension, obesity, diabetes mellitus, impaired thyroid function, connective tissue diseases, malignancy, previously diagnosed symptomatic or asymptomatic coronary artery disease, valvular heart diseases (except minimal valvular insufficiency), neurological and psychiatric diseases, and taking certain drug regimens (e.g., beta blockers, calcium channel blockers and antiarrhythmic drugs) were excluded from the study. When the patient with FMS had a tender point on the chest, we used the treadmill exercise test to exclude angina. Those patients with additional bone and joint pathologies unable to perform treadmill test and who could not tolerate position changes during autonomic tests were also excluded from the study.

The patients who were diagnosed with primary FMS in the PMR department, and who met the inclusion criteria of the study were transferred to the Department of Cardiology. A 12-lead electrocardiogram (ECG) and 24-hour Holter recordings (Delmar-Impresario Medical Systems, Irvine, California, USA) were collected. Posteroanterior chest radiography, color Doppler echocardiography (Ge-Vivid 7 Pro, General Electric, Florida, USA) and treadmill test (Quinton 4500 treadmill, Seattle, USA-Bruce protocol) were also performed.

Autonomic tests

The patients were rested for 15 minutes in supine position at the beginning of the test. Subsequently, arterial blood pressure measurement and a 12-channel ECG recording were performed in all patients. Afterwards, skin was rubbed before applying electrodes and then a Holter device was affixed and starting time was adjusted to minute sensitivity. Holter recordings were done on a three-derivation system. After turning on the Holter recordings, we performed orthostatic stand and supine test, inspiration-expiration and Valsalva tests.

Measurement of 24-Hour HRV

Recordings were performed with 24-hour Holter monitoring and analyzed with Delmar-Impresario system and software (Delmar-Impresario Medical Systems, Irvine, California, USA). The analyzed data and standard measurement criteria were evaluated within the scope of the published guidelines (11) (Table 1).

HRV parameters were measured both in the frequency domain (power spectral analysis) and in the time-domain. We also calculated the logarithmic values of all HRV measurements to determine logarithmic changes in the parameters.

Measurement of day and night HRV

HRV parameters were analyzed at day and night. We defined "day" as the time period between 06:00 and 22:59 and "night" as the period between 23:00 and 05:59. We obtained (Table 1) the time-domain analysis parameters SDNN, SDNN index, and rMSSD for day and night periods and day-night differences. The parameters of frequency domain HRV analysis (VLF, LF, HF, total power parameters, and LF/HF, LFn and HFn ratios) for day and night periods were evaluated separately. The following parameters were also calculated: HF_{Day}/HF_{Night}, $LF/HF_{Day}/LF/HF_{Night}$, LFn_{Day}/LFn_{Night}, HFn_{Day}/HFn_{Night} ratios for detection of day-night fluctuations of sympathovagal balance and parasympathetic activity between patient and control groups.

Orthostatic tests

Stand test: Patients were asked to stand up rapidly while resting in a supine position. The starting time of the stand test was recorded in minute sensitivity. After having the patients stand, pulse rates were recorded separately for each minute. Patients were kept in standing position for 2 more minutes and then supine test was started. Total time of stand test was limited to 5 minutes.

Supine test: Patients in the standing position were asked to lie down rapidly. The starting time of the supine test was recorded in minute sensitivity. Pulse rates were again recorded separately for each minute.

Inspiration-Expiration test

Patients were asked to inspire and expire deeply each for 6 times per minute in the sitting position. The starting and ending times of the tests were recorded. Total time of the inspiration-expiration test was limited to 1 minute.

Valsalva test

Patients were asked to do the Valsalva maneuver throughout a minimum of 15 seconds in the sitting position. The starting and ending times of the test were recorded.

At the end of the autonomic tests, measurement of arterial blood pressure and an ECG recordings were repeated and then patients were discharged and called back at the end of the 24-hour period. The recordings of 24-hour Holter monitoring were analyzed. After routine evaluations of Holter recordings (e.g. basic rhythm determination and evaluation of arrhythmias, ST segment levels), the measurement and evaluation of HRV parameters were performed.

The 24-hour period and the first 2-minute and 5-minute periods of autonomic tests from the beginning of stand and supine tests were evaluated separately. Although Valsalva and inspiration-expiration test lasted only 1 minute or less, we evaluated the first 2-minute and 5-minute periods from the beginning of these tests.

Detection and evaluation of arrhythmias

Detection and evaluation of arrhythmias (supraventricular extrasystoles (SES), supraventricular tachycardia (SVT), ventricular extrasystoles (VES) and ventricular tachycardia (VT)) were performed with 12-lead ECG and 24-hour Holter monitoring records with reference to classic electrocardiographic criteria (12-14). Sinus or respiratory arrhythmias were ignored. All forms of conduction abnormalities were accepted as exclusion criteria.

Statistical analyses

SPSS 15 Statistics Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) was used for the analyses. Normally distributed data were expressed as mean ± standard deviation (SD) and non-normally distributed data were expressed as median (minimum-maximum) values. Differences between the means and median values of the groups were determined using Student t-test and Mann-Whitney U test, respectively. Differences in the prevalence of arrhythmia types between control and FMS groups were determined using Pearson Chi-Square test. The correlation of data was tested by using Spearman correlation analysis. A p value of 0.05 was considered statistically significant.

Results

The anthropometric characteristics of the 50 patients and 30 controls included in the study are given in Table 2. Laboratory tests including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, complete blood count, biochemical tests,

Table 1. The concomitance of each category of nonadherence

Frequency Domain HRV Analysis Parameters	Power Spectrum
Very Low Frequency, (VLF), msec^2	(0.003 - 0.04) Hz
Low Frequency, (LF), msec^2	(0.04 - 0.15) Hz
High Frequency (HF), msec^2	(0.15 - 0.40) Hz
Total Power (TP), msec^2	(0 - 0.40) Hz
LF/HF Ratio	LF Power / HF Power
LFn (Normalized LF)	LF/ (total power-VLF)x100
HFn (Normalized HF)	HF/ (total power-VLF)x100
Time domain HRV analysis parameters	Definitions
SDNN, msec	Standard deviation of all normal RR intervals in the 24-h Holter
SDNNi, msec	Mean of the standard deviations of all normal RR intervals for all five minute segments of the entire recording.
rMSSD, msec	Square root of the mean differences between successive RR intervals.
pNN50, %	Percentage of differences between successive RR intervals that are >50 milli seconds, computed over the 24-h Holter

Table 2. Demographic and anthropometric characteristics of subjects

Parameters	Patients (n=50)	Controls (n=30)	p*
Age, years	38±7	36±8	NS
Height, cm	160±5	162±6	NS
Weight, kg	70±11	67±16	NS
Body mass index, kg/m^2	27.4±4.4	25.8± 6.4	NS
Waist, cm	85±18	87±21	NS

Data are presented as mean±SD
*Unpaired Student t-test for independent samples
NS - non-significant, p> 0.05.

Brucella agglutination, antinuclear antibody (ANA), anti-DNA tests, and hormonal tests (thyroid function tests, free cortisol levels, estrogen levels) were in normal ranges in all patients.

HRV and autonomic tests

24-hour HRV: The results of 24-hour HRV measurements of patient and control groups are shown in Table 3. No statistically significant difference was observed in daily maximum, minimum and mean heart rate values between groups. The HF power was significantly decreased (p=0.017) and LF/HF ratio was significantly higher in the patient group (p=0.001) as compared with control group. In time-domain analysis, pNN50 was found to be significantly decreased in the patient group (p=0.042).

Day and Night HRV: The results of HRV measurements in the patient and control groups for day and night periods are given in Tables 4 and 5 respectively. Although no significant differences were detected between the patient and control groups for the day period, significant differences were detected between the two groups for the night period. HF_{Night} and HFn_{Night}, in the patient group were found lower than in the control group (p=0.001 and p<0.001, respectively). In contrast, LFn_{Night}, LF/HF_{Night} in the patient group were higher than in the control group (p<0.001 and p<0.001, respectively). The LF/HF_{Night} was also higher in the patient group (p<0.001).

There were statistically significant differences in regards to day-night difference and ratios of HRV: the HF_{Day}/HF_{Night}, $LF/HF_{Day}/LF/HF_{Night}$, $LF(n)_{Day}/LF(n)_{Night}$, and $HF(n)_{Day}/HF(n)_{Night}$ ratios between the patient and control groups (p=0.047, p=0.004, p=0.001 and p=0.008, respectively).

Orthostatic tests

There were no statistically significant differences between the patient and control groups in terms of the stand test systolic-diastolic and supine test systolic-diastolic arterial blood pressure measurements (p>0.05).

Stand test: Significant differences were found in HF power (28.7 $msec^2$ (13.0- 83.9) vs 62.0 $msec^2$ (39.6- 158.9), p=0.003) and logarithmic value of HF power (Log HF) (1.50±0.49 msec2 vs.1.86±0.45 $msec^2$, p=0.002) at the 2nd minute of stand test between the patient and control groups. On the other hand,

Table 3. Results of 24-hour heart rate and heart rate variability (HRV) measurements in patients and controls

Variables	Patients (n=50)	Controls (n=30)	p*
Maximal heart rate, beats/min	132±17	134±16	NS
Minimal heart rate, beats /min	54±7	55±7	NS
Mean heart rate, beats /min	77±9	76±9	NS
Frequency Domain Analysis			
LF/HF	2.22±0.18	1.22±0.12	<0.001
LFn	0.64±0.02	0.49±0.02	<0.001
HFn	0.35±0.02	0.50±0.02	<0.001
Time Domain Analysis			
pNN50, %	8.1 (0.9-29.6)	12.7 (0.9-49.4)	0.042
rMSSD, msec	34.0 (21.1-67.4)	37.4 (19.2-135.3)	NS

The values are expressed as mean±SD and median (min-max)
*Unpaired Student t-test for independent samples and Mann-Whitney U test
HFn - normalized high frequency power, LFn - normalized low frequency power, NS - non-significant, pNN50 - percentage of differences between successive RR intervals that are >50 milliseconds, computed over the 24-h Holter, rMSSD - square root of the mean differences between successive RR intervals

Table 4. Heart rate variability parameters detected in day period (06:00-22:59)

Variables	Patients (n=50)	Controls (n=30)	p*
Frequency Domain Analysis			
LF/HF	3.59±2.02	2.90±2.02	NS
LFn	0.73±0.15	0.68±0.15	NS
HFn	0.27±0.15	0.32±0.15	NS
Time domain analysis			
rMSSD, msec	28.2 (15.3-61.7)	28.8 (18.2-86.5)	NS

The values are expressed as mean±SD and median (min-max)
*Unpaired Student t-test for independent samples and Mann-Whitney U test.
HFn - normalized high frequency power, LFn - normalized low frequency power, NS - non-significant, rMSSD - square root of the mean differences between successive RR intervals

LF/HF ratio (4.7 (2.8-10.1) vs. 3.34 (2.1-6.8), p=0.037) and its logarithmic value (Log LF/HF) (0.72±0.47 vs. 0.46±0.43, p=0.018) were significantly higher at the 2nd minute of stand test in the patient group as compared with control group . There were no significant differences in HF power and LF/HF ratio at the 5th minute of stand test between the groups (p>0.05).

Supine test: The HF power (2nd minute-58.5 msec^2 (30.4-123.2) vs. 139.6 msec^2 (33.5- 381.7), p=0.019, 5th minute-39.7 (22.8-79.7) msec^2 vs. 64.3 (34.1-147.7) msec^2, p=0.005) and Log HF (2nd minute-1.72±0.54 vs. 2.09±0.66, p=0.007, 5th minute-1.62±0.45 vs. 1.81±0.39, p=0.002) at the 2nd and 5th minutes of supine test were significantly lower in patients with FMS than in controls.

There was no significant difference in LF/HF ratio at the 2nd minute of supine test between the patient and control groups (p>0.05). On the other hand, there were significant differences in LF/HF ratio (for FMS group - 2.5 (1.4- 3.8); for control group-1.3 (1.0-2.1), p=0.001) and Log LF/HF (for FMS group-2.16±0.55 and for control group - 1.78±0.50; p=0.003) between the groups at the 5th minute of supine test.

Inspiration-Expiration and Valsalva tests

Significant differences in HF values between groups were observed at the 5th minute of inspiration-expiration test (for FMS group- 35.2 msec^2 (15.9- 60.6); for control group-56.4 msec^2 (29.2-89.8), p=0.030) and at the 5th minute of Valsalva test (for FMS group-27.9 msec^2 (17.8- 49.6); for control group-55.1 msec^2 (17.0-103.3), p=0.032).

Arrhythmia prevalence

The prevalence of SES was higher in the FMS group as compared with control group (48% vs. 23.3%, p=0.028). Similarly, the mean number of SES was higher in the patient group than in control one (187.3±62.3 vs.127.1±21.4, p=0.019).

Also, in the FMS group, SVT was detected in 5 (10%) of the 50 patients. There was no SVT attack in the control group. Detected tachycardia attacks had narrow QRS and regular R-R intervals. All of them had sudden onset and ending and P wave was found after QRS complex. We evaluated the tachycardia attacks and diagnosed AV nodal reentrant tachycardia (AVNRT) in all patients which were diagnosed as SVT. At the same time, all these patients had an AVNRT attack in the night period. We also detected that night period attacks in these patients were slow and short.

Tachycardia characteristics of 5 FMS patients

The number and characteristics of SVT attacks of the patients with FMS are shown in the Table 6. Although the FMS group patients had SVT, there were no statistically significant differences detected between the two groups (p=0.075). In the FMS group, VES were detected in 11 (22%) of the total 50 patients. In controls, VES were detected in only 2 (6.7%) of the 30 participants. However, there were no statistically significant differences between the two groups (p=0.074,). No VT was detected in any of the groups.

Table 5. Heart rate variability parameters detected in night period (23:00-05:59)

Variables	Patients (n=50)	Controls (n=30)	p*
Frequency domain analysis			
LF/HF	2.78±1.97	1.15±0.77	<0.001
LFn	0.66±0.15	0.47±0.16	<0.001
HFn	0.34±0.15	0.53±0.16	<0.001
Time domain analysis			
rMSSD , msec	40.4 (20.1-94.7)	48.1 (18.9-213.0)	NS

The values are expressed as mean±SD and median (min-max)
*Unpaired Student t-test for independent samples and Mann-Whitney U test
HFn - normalized high frequency power, LFn - normalized low frequency power, NS - non-significant, rMSSD - square root of the mean differences between successive RR intervals

Table 6. Supraventricular tachycardia (SVT) characteristics of the patients with FMS

Patients	Day period (06:00-22:59) SVT attacks			Night period (23:00-05:59) SVT attacks		
	Number	Duration, sec	R-R interval, msec	Number	Duration, sec	R-R interval, msec
Patient 1	1	8	380	1	6	420
Patient 2	1	10	390	1	6	430
Patient 3	-	-	-	1	6	420
Patient 4	-	-	-	1	7	430
Patient 5	-	-	-	1	5	410
				1	5	430

Correlations between Autonomic Activity and Arrhythmias

Correlations between the number of different arrhythmia types in 24 hour period and HRV parameters are shown in Table 7. There were statistically significant positive correlations between arrhythmia types and sympathetic activity parameters for 24 hour and Night periods (LF/HF_{24Hour}, LF/HF_{Night}) ($p<0.05$). On the other hand, $LFHF_{Day}$/ $LFHF_{Night}$ ratio negatively correlated with all arrhythmia types.

Discussion

In this study, we found that there were increased sympathetic and diminished parasympathetic activities in the patients with FMS for 24- hour, day and night periods and during the autonomic tests. There were also blunted autonomic day and night period fluctuations in FMS group. Moreover, we detected that the patients with FMS had increased SES prevalence. On the other hand, all arrhythmia types were found as positively correlated with oversympathetic activity and blunted autonomic fluctuation in the patients with FMS.

It is well known that the basic pathophysiologic mechanisms of FMS occur due to neurohormonal disturbances and autonomic dysfunction (14-20, 31). It is considered that FMS is a stress-related disorder (14). The effects of alterations in hypothalamic-pituitary-adrenal axis (HPAA) and sympathetic nervous system on homeostasis and physiopathologic relation of FMS with this axis were shown previously (14-17, 20, 31).

Although there is increasing interest about cardiovascular effects of autonomic dysfunction in many types of neurohormonal disturbances, especially related with HPAA (31-34), there is insufficient data in the literature about cardiovascular effects of autonomic dysfunction in FMS. Some of the FMS symptoms like sleep disturbances, fatigue, orthostatic intolerance, and excessive rate of syncope were attributed to autonomic dysfunction in FMS patients by some authors (28-30). Although increased sympathetic and decreased parasympathetic activity were described in FMS by evaluation of 24-hour HRV parameters in many of the previous studies (1-5), Furlan et al. (28) described an autonomic dysregulation in FMS patients that included not only increased sympathetic and decreased parasympathetic activity, but also a lack of increased sympathetic discharge to vessels and decreased cardiac vagal activity. Friederich et al. (29) attributed these autonomic changes to the presence of reduced baroreceptor-mediated activation of the sympathetic nervous system and a hyporeactive sympathetic nervous system. They showed a hyporeactive stress system in FMS patients for both peripherally and centrally mediated stimulation of the sympathetic nervous system.

Actually, the effects of increased sympathetic activity on the cardiovascular system actually comprise a complex response

Table 7. Correlations between the number of different arrhythmia types in 24 hour period and HRV parameters

	24 hour period HRV parameters				
	HF	LF/HF	LFn	HFn	LFHFDay/LFHFNight
SES number	NS	r= 0.398 p=0.027	r= 0.389, p=0.030	r= - 0.389 p=0.030	r= - 0.610 p=0.030
SVT number	NS	r= 0.207 p=0.066	r= 0.216, p=0.055	r= - 0.216 p=0.055	r= - 0.324 p=0.006
VES number	NS	r= 0.505 p=0.030	r= 0.525, p=0.025	r= - 0.525 p=0.025	r= - 0.663 p=0.007
	Day period (06:00-22:59) HRV parameters				
	HF	LF/HF	LFn	HFn	-
SES number	NS	NS	NS	NS	-
SVT number	NS	NS	NS	NS	-
VES number	NS	NS	NS	NS	-
	Night period (23:00-05:59) HRV parameters				
	HF	LF/HF	LFn	HFn	-
SES number	r= - 0.376 p=0.037	r= 0.546 p=0.001	r= 0.518 p=0.003	r= - 0.518 p=0.003	-
SVT number	NS	r= 0.344 p=0.003	r= 0.269 p=0.024	r= - 0.269 p=0.024	-
VES number	NS	NS	NS	NS	-

Spearman correlation analysis
HF - high frequency power, HFn - normalized high frequency power, HRV – heart rate variability, LF - low frequency power, LFn - normalized low frequency power, NS - non-significant, SES - supraventricular extrasystole, SVT - supraventricular tachycardia, VES - ventricular extrasystole

regarding the interaction of an organism to stress autoregulation of the cardiovascular system (15-20), especially heart rate and blood pressure, which are strictly controlled by the autonomic nervous system (ANS) as a response to stress factors. At this point, HRV parameters are extremely useful for indirect quantitative evaluation of autonomic functions (11). Thus, HRV parameters are frequently used in clinical practice for indirect quantitative evaluation of autonomic functions.

We also used HRV parameters for indirect evaluation of autonomic activities. In our study, HF, pNN50 and rMSSD values, the HRV parameters that are related with parasympathetic activity, were found to be significantly decreased in the FMS group over a 24-hour period. Further, increased LF/HF ratio and normalized LF values were also clues for the presence of increased sympathetic activity in the same period. Our study results support previous studies (1-5).

Cohen et al. (1) also showed the presence of abnormal sympathovagal balance during orthostatic tests. They reported that the patients with FMS at rest are characterized by sympathetic hyperactivity and concomitantly reduced parasympathetic activity. During postural changes, patients demonstrated an abnormal sympathovagal response.

Our orthostatic test results also support the results of that study. We determined decreased parasympathetic and increased sympathetic activity during orthostatic stress (stand and supine tests), inspiration-expiration and Valsalva test in FMS patients. Differences in sympathovagal balance (LF/HF) between the patient and control groups became especially evident during orthostatic tests.

Furlan R et al. (28) showed that patients with FMS had an overall enhancement of cardiovascular sympathetic activity while recumbent. Our results also support those of Furlan's study. We also detected that the normalization time of increased sympathetic activity after supine test was longer in FMS patients than in the control group.

Recently, the issue of nocturnal autonomic changes in FMS has emerged as a research area of increasing interest. In spite of this, there are insufficient data in the literature about the changes in nocturnal autonomic activity and the clinical aspects of this autonomic circadian disturbance in FMS patients. In physiological conditions, nocturnal sympathetic activity is less than diurnal sympathetic activity and additionally, parasympathetic activity is dominant in the nocturnal period (35). On the other hand, some studies have shown that there are severe autonomic changes in FMS. Firstly, Martínez-Lavín et al. (30) reported increased sympathetic activity during the nocturnal period in FMS patients. They attributed the sleep disturbances and fatigue that occur in FMS to this abnormal nocturnal autonomic balance. We also detected in this study autonomic dysregulation revealing increased sympathetic and decreased parasympathetic activity, especially at night, in FMS patients when compared with the control group.

On the other hand, it is well known that arrhythmia could reflect an autonomic dysfunction if no other arrhythmia predisposition factor exists (21-25). Although there are many studies showing enhancing effects of increased sympathetic activity on various types of arrhythmias in many different pathological conditions, data about the arrhythmia prevalence in FMS, in which increased sympathetic activity is already shown, are lacking.

We found in the present study that the number of SES was higher in the patient group compared to the controls. SES and VES were found to be positively correlated with increased sympathetic activity and negatively correlated with parasympathetic activity for all periods. However, we detected that night time sympathetic activity (LF/HF_{Night}) was the most effective factor for the number of SES and day time sympathetic activity (LF/HF_{Day}) for the number of VES. It seems that increased night time sympathetic activity in FMS causes an increased number of SES. On the other hand, no statistically significant difference was determined in day time sympathetic activity between the FMS group and the controls as well as no difference in the number of VES.

There were no statistically significant differences in the number of SVT attacks between the patient and control groups. SVT was found in only five patients. However, some characteristics of these patients were rather important. All patients had night time SVT attack. It could be attributed to the increased sympathetic activity in the night time period in the FMS group. One of the important data was that SVT attacks were negatively correlated with day time - night time sympathetic activity ratio. Any decrease in fluctuation of the sympathetic activity between day and night time periods could be a triggering or at least a preparatory factor for SVT.

Although some authors proposed a positive relationship between FMS and enhanced mortality rate (26, 27), the exact mechanisms of this condition are still unclear.

Autonomic activity abnormalities during sleep may cause increased susceptibility of the myocardium (9). In our study, SVT attacks detected in patients mainly occurred during the night. This condition could also be attributed to nocturnal oversympathetic activity.

Although there were no exact proofs about the clinical importance or pathophysiologic mechanisms of arrhythmia in FMS, we considered that autonomic dysfunction, oversympathetic activity and autonomic circadian changes may enhance the vulnerability of the myocardium and these factors could result in higher arrhythmia tendency in FMS (21-27).

Limitations of the study

Our study focused on a small number of patients and controls. At this point, it was a pilot study aimed to reveal the relationships between autonomic changes and arrhythmia in a small group of FMS patients. Therefore, large-scale studies are warranted to elucidate the pathophysiologic mechanisms and clinical importance of autonomic dysfunction and arrhythmia in FMS.

Conclusion

Increased sympathetic and decreased parasympathetic activity and some autonomic circadian activity changes are present in FMS. All these changes might be effective on

increased arrhythmia prevalence in FMS. It could thus also be concluded that FMS patients must be closely followed for arrhythmias.

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