

Abnormal Sympathovagal Balance in Men with Fibromyalgia

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ABSTRACT. *Objective.* It is possible that there are differences in clinical manifestations between men and women with fibromyalgia syndrome (FM), especially in autonomic dysfunction; we assessed the interaction between the sympathetic and parasympathetic systems in postural change in men with FM using power spectral analysis (PSA) of heart rate variability (HRV), and investigated the pathogenesis of the orthostatic intolerance.

Methods. We studied 19 men with FM and 19 controls matched for age and sex. A high resolution electrocardiogram was obtained in supine and standing postures during complete rest. Spectral analysis of R-R intervals was done by the fast Fourier transform algorithm.

Results. PSA of HRV revealed that men with FM at rest are characterized by sympathetic hyperactivity and concomitantly reduced parasympathetic activity. During postural changes, male patients demonstrated an abnormal sympathovagal response. These results provide the physiological basis for the orthostatic intolerance in men with FM.

Conclusion. This report of autonomic dysfunction in men with FM revealed an abnormal autonomic response to orthostatic stress. This abnormality may have implications regarding the symptoms of FM. (J Rheumatol 2001;28:581-9)

Key Indexing Terms:

FIBROMYALGIA SYNDROME
HEART RATE VARIABILITY

AUTONOMIC NERVOUS SYSTEM
DEPRESSION

ANXIETY
POWER SPECTRAL ANALYSIS

Fibromyalgia syndrome (FM) is an idiopathic, chronic pain syndrome characterized by widespread nonarticular musculoskeletal pain and generalized tender points^{1,2}. It affects women more frequently than men². The pathophysiology of FM is not clear; however, suggestions have included central neurochemical pain or peripheral soft tissue mechanisms³⁻⁶.

There is some evidence suggesting autonomic nervous system involvement in the this syndrome⁷⁻¹². Our findings, using power spectral analysis (PSA), of heart rate variability (HRV) in women with FM show that the basal autonomic state of patients with FM is characterized by increased sympathetic and decreased parasympathetic tones¹³.

Spectral analysis of HRV is a simple, noninvasive method for quantifying the activity of autonomic nervous system functions¹⁴. PSA of HRV has been used to explore

dynamic mechanisms in the cardiovascular system, and appears to provide a quantitative evaluation of the sympathovagal interaction that modulates cardiovascular function¹⁵. It has been shown that harmonic oscillations in heart rate are concentrated into at least 2 distinct bands. The one referred to as the low frequency band (LF) is affected by the oscillatory rhythm of the baroreceptor system and is mediated by sympathetic influences. The high frequency band (HF) has respiration as the primary rhythmic stimulus and is mediated by changing levels of parasympathetic tone. HRV involves complex interaction between several mechanisms to maintain heart rate and blood pressure within normal limits. In healthy subjects this can include the reaction to activity or postural changes¹⁶, physical exercise¹⁷, and mental/emotional stress¹⁸. HRV has been proven useful in the study of various diseases, such as hypertension¹⁹, diabetic neuropathy²⁰, heart failure²¹, myocardial ischemia²², and acute myocardial infarction²³.

We explored the application of PSA of HRV in studying the dynamics of the interaction between the sympathetic and parasympathetic systems in men with FM compared to healthy matched control subjects under the same conditions.

MATERIALS AND METHODS

Patients. Since 1990, 630 patients with FM have been followed in the outpatient rheumatology service at Soroka Medical Center, Beer-Sheva. Forty of the 630 patients (6.3%) were men. Nineteen patients diagnosed as

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having FM according to the criteria of the American College of Rheumatology² and fulfilling the inclusion/exclusion criteria consented to participate. All were aged 33 to 60 years (mean 45.8 ± 7.1). Ten were nonsmokers and 9 smokers. The mean level of education was 11.0 ± 4.0 years, 54% were employed, and the mean disease duration was 8.0 ± 9.0 years.

Exclusion criteria consisted of current or recent substance abuse disorders, psychotic symptoms, significant cognitive impairment likely to interfere with study procedures or informed consent, severe or acute concomitant medical illness, such as structural cardiac abnormalities or inflammatory rheumatic disease, or any other illness known to affect the autonomic nervous system. Any psychotropic or other medications known to alter autonomic activity for at least 4 weeks prior to the study, including antihypertensive drugs, tranquilizers, or antidepressants, also disqualified potential subjects.

Controls. The control group consisted of 19 healthy volunteers matched for age, sex, smoking, and time of day of electrocardiogram (ECG) recordings. They were chosen from a list of hospital personnel. All controls were healthy, with no serious or disabling coexisting diseases as evidenced from their medical records and examination. All were screened for FM symptoms. Participants had not taken any psychotropic or other medications known to alter autonomic activity for at least 4 weeks prior to the study.

The study was approved by the Helsinki Ethics Committee of the hospital. All participants gave written consent after receiving detailed information on the study.

Electrocardiogram recording. The ECG recording was obtained by connecting the subjects to a Holter monitor in a supine position during complete rest (Oxford 4-24). Twenty minute segments of lead II ECG were amplified, digitized, and stored using a computer software system (Biopac System, Inc., Santa Barbara, CA, USA). To minimize anticipatory stress, the room was quiet and isolated from patient traffic, and ambient temperature was maintained at $25 \pm 1^\circ\text{C}$ (to eliminate variations in temperature that might activate thermoregulatory mechanisms and change distribution of power frequencies in various bands). A detailed explanation of the procedure was given. After a stabilization period (at least 15 min), recordings were obtained during supine rest (20 min). The same recording was made 5 min after adopting the upright position. Subjects were instructed to breathe normally, and respiratory rate was measured. The positional changes at which ECG recordings were made are termed "postural stages."

ECG data were digitized at a rate of 500 Hz (width pass 0.05–35 Hz). The ECG signal was converted into an event series, which required the measurement of R-R intervals (256 consecutive RR intervals). Premature beats and noise were excluded both automatically and manually, and only segments with > 90% qualified beats were included in the analysis. Representing this series as a function of the R wave time of occurrence created a non-uniformly sampled event series. Therefore, the second phase of the algorithm was interpolated. Finally, analyses of HRV, fast-Fourier transform, and power spectral density (PSD) (calculated as millisecond squared/Hz) were performed using signal processing software as described²⁴. We divided the power spectrum into 2 major frequency ranges: LF bands (0.04–0.15 Hz) and HF bands (0.15–0.5 Hz). The integral of the power spectrum within each region was calculated (Simpson integration).

To test the hypothesis concerning the involvement of comorbid psychiatric symptoms such as depression and anxiety, the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale were applied.

Hamilton Depression Rating Scale (HAM-D). The HAM-D²⁵ is a 23 item scale that measures the presence and severity of depression. Each symptom is rated on a defined scale (0 to 4). A high numeric rating reflects a greater degree of symptom severity.

Hamilton Anxiety Rating Scale (HAM-A). HAM-A²⁶ is a clinician rated instrument that measures the presence and severity of anxiety. This instrument consists of a 14 symptom scale. Each symptom is rated on a defined scale (0 to 4). Here, too, a high numeric rating reflects a greater degree of symptom severity.

Diagnostic criteria for depression and anxiety require a score of 20 or greater on the HAM-D and HAM-A scales.

The questionnaires were filled out in the presence of an interviewer and subjects were assisted in answering the questions, if needed. The interviewer made sure that all subjects clearly understood the content of each item and the different aspects of various components.

Statistical analysis. As all HRV indexes were skewed, a natural logarithmic transformation was used to normalize the data adequately. To compare effects in groups (FM vs controls) and in the 2 different stages (supine and standing), the variables were analyzed by analysis of covariance (2 way ANCOVA repeated measures) with age as the covariate. Age was entered as a covariate because HRV decreases with increasing age ($r = -0.73$, $r^2 = 0.53$, $F(1,8) = 7.83$, $p < 0.02$). Post hoc comparisons employed Scheffe's test.

Responses to change of posture were determined by subtracting the subject's results on standing from those in a supine posture, and this difference was defined as the delta value. Comparison of the differences between upright and supine positions was by Student's t test for matched samples, while patients and controls were compared by t test for independent samples.

RESULTS

Power spectral analyses in male patients with FM versus controls are summarized in Table 1 and in Figures 1 and 2. In the supine posture, HR was significantly higher in patients compared to controls at the same posture ($p = 0.000035$). Neither group showed a significant change in HR between the postural stages. The increase in mean HR while standing in the control group was statistically significant ($p = 0.0178$). While standing, patients had significantly higher HR than controls ($p = 0.042$).

Throughout all postural stages of the trial, the FM population showed significantly less HRV than the controls ($p = 0.000084$). During standing, the control group showed robust responses in HRV ($p = 0.025$), but FM patients did not.

Patients had significantly higher LF components in supine posture compared to controls in the same posture ($p = 0.00005$). During standing, the control group showed normal responses in LF ($p = 0.0017$), but FM patients did not.

Patients had significantly lower HF power spectrum density relative to controls in supine position ($p = 0.00005$). The control group showed a significant difference between supine and standing ($p = 0.0017$) in the HF component, but the patients did not.

The delta value of the LF and HF power of the patients was significantly different from that of controls ($F = 0.0045$, $p = 0.0084$, respectively) (Table 2, Figure 3).

There were no changes in the respiratory rate (range 13–17 cyclic/min) in both groups at all stages. This implies that any significant difference in HF can be attributed to nonrespiratory effects on parasympathetic tone.

Patients had significantly higher total HAM-D scores (mean and SD: 30.1 ± 5.82 vs 8.65 ± 4.46) and HAM-A scores (30.2 ± 6.9 vs 8.09 ± 2.75) than controls (HAM-D scores, $F = 218.63$, $p = 0.0000$; HAM-A scores, $F = 215.34$, $p = 0.0000$).

Table 1. Power spectral analysis in male FM patients vs controls.

	Male FM Patients (n = 19) Supine I	Male FM Patients (n = 19) Standing II	Control (n = 19) Supine III	Control (n = 19) Standing IV	Post Hoc Scheffe test
Time domain					
Mean R-R interval ¹	733.4 ± 85.9	707.553 ± 46.52	942.82 ± 138.04	15.51 ± 143.5	I,II, IV ≠ III
Standard Deviation ²	27.04 ± 1.54	26.59 ± 0.9	30.635 ± 2.14	28.45 ± 2.5	I,II, IV ≠ III
Variance ³	748.03 ± 85.95	722.14 ± 46.53	957.5 ± 138.04	830.1 ± 143.4	I,II, IV ≠ III
Absolute (log) power values of the frequency bands: (ms ²)					
LF ⁴	3.33 ± 0.017	3.32 ± 0.02	3.41 ± 0.08	3.34 ± 0.042	I,II, IV ≠ III
HF ⁵	4.41 ± 0.2	4.48 ± 0.3	3.99 ± 0.24	3.33 ± 0.316	I,II, IV ≠ III
Frequency domain					
Power (normalized units)					
LF, % ⁶	91.8 ± 3.6	92.5 ± 3.9	77.3 ± 12.5	88.6 ± 8.15	I,II, IV ≠ III
HF, % ⁷	8.2 ± 3.6	7.5 ± 3.9	22.6 ± 12.5	11.4 ± 8.15	I,II, IV ≠ III
LF/HF ⁸ (The mean of individual ratios)	13.6 ± 6.3	18.06 ± 14.9	4.8 ± 3.1	13.12 ± 9.3	I, II ≠ III
Heart rate ⁹ (bpm)	82.75 ± 8.6	85.2 ± 5.7	64.7 ± 7.9	75.6 ± 12.3	I,II, IV ≠ III II ≠ IV

Results are expressed in normalized units, as mean and SD. Two way ANCOVA repeated measure: between: groups (FM and control) within: posture (supine vs standing), covariates — age and smoking.

¹Group effect: F = 44.265, p = 0.00000; posture effect: F = 7.95, p = 0.00785, NS.

²Group effect: F = 47.32, p = 0.00000; posture effect: F = 8.29, p = 0.0067, NS.

³Group effect: F = 44.265, p = 0.00000; posture effect F = 7.95, p = 0.0079, NS.

⁴Group effect: F = 24.83, p = 0.00002; posture effect: F = 10.2, p = 0.003; interaction: F = 8.1, p = 0.0074.

⁵Group effect: F = 18.56, p = 0.000013; posture effect: F = 14.3, p = 0.0006; interaction: F = 6.54, p = 0.015.

⁶Group effect: F = 25.95, p = 0.000012; posture effect: F = 10.8, p = 0.0023; interaction: F = 8.3, p = 0.00665.

⁷Group effect: F = 25.95, p = 0.000012; posture effect: F = 10.8, p = 0.0023; interaction: F = 8.3, p = 0.00665.

⁸Group effect: F = 8.5, p = 0.0062; posture effect: F = 9.4, p = 0.0041; interaction NS.

⁹Group effect: F = 52.4, p = 0.0000; posture effect: F = 8.8, p = 0.0054; interaction NS.

DISCUSSION

We observed that supine male patients with FM had significantly higher heart rate and lower heart rate variability values than controls. This reflects a basal autonomic state of hyperactivation, characterized by increased sympathetic and decreased parasympathetic tone. These findings support our results in women with FM¹³ and those of other research groups, which have shown that patients with FM have hyperactivity of the sympathetic nervous system^{7,11}.

Our second finding is that postural change (from supine to standing) is accompanied by an abnormal sympathetic response in male patients with FM compared to healthy controls. The observed autonomic (sympathetic and parasympathetic) response to postural change of the control group is taken to represent the normal reaction of a well balanced autonomic nervous system response — increased LF power and decreased HF power, with an adequate sympathovagal balance^{16,27-29}. Upon standing, the rapid migration of blood from the thorax to the lower parts of the body initially results in a decrease in venous return and a fall in cardiac output. These changes promptly activate compen-

satory mechanisms, among which the baroreflex is of primary importance, and a decrease in vagal tone and a concomitant increase in sympathetic tone, resulting in an increase in heart rate and total peripheral resistance.

In light of evidence that patients with FM had an abnormal drop in blood pressure in stage 1 of upright tilt¹⁰, we may speculate that other factors may be involved in the abnormal sympathovagal response to postural change. These include decreased responsiveness of the baroreflex to fluctuations in blood pressure^{30,31} and increased venous pooling due to disuse atrophy of the leg muscles, increased leg compliance³², and a loss of venomotor tone³³ that results in decreased cardiac preload. Alternatively, the diminished or absent sympathetic response to postural change in patients with FM may reflect a state of chronic autonomic overstimulation at rest, preventing further response. Finally, the observed disparity in sympathetic response in the different studies in response to physiological stress may be the result of limitations of the instrument, i.e., a ceiling effect.

We postulate that the abnormality in the overactivity of

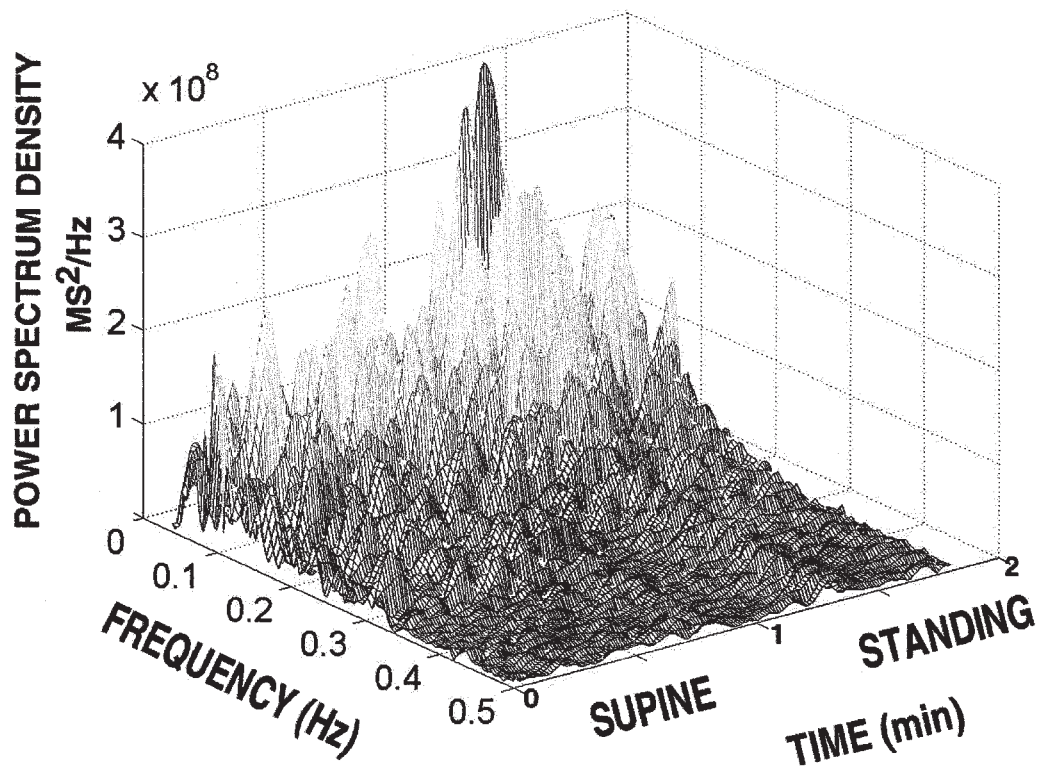


Figure 1. Power spectrum density analysis of HRV in male patients with FM supine and standing.

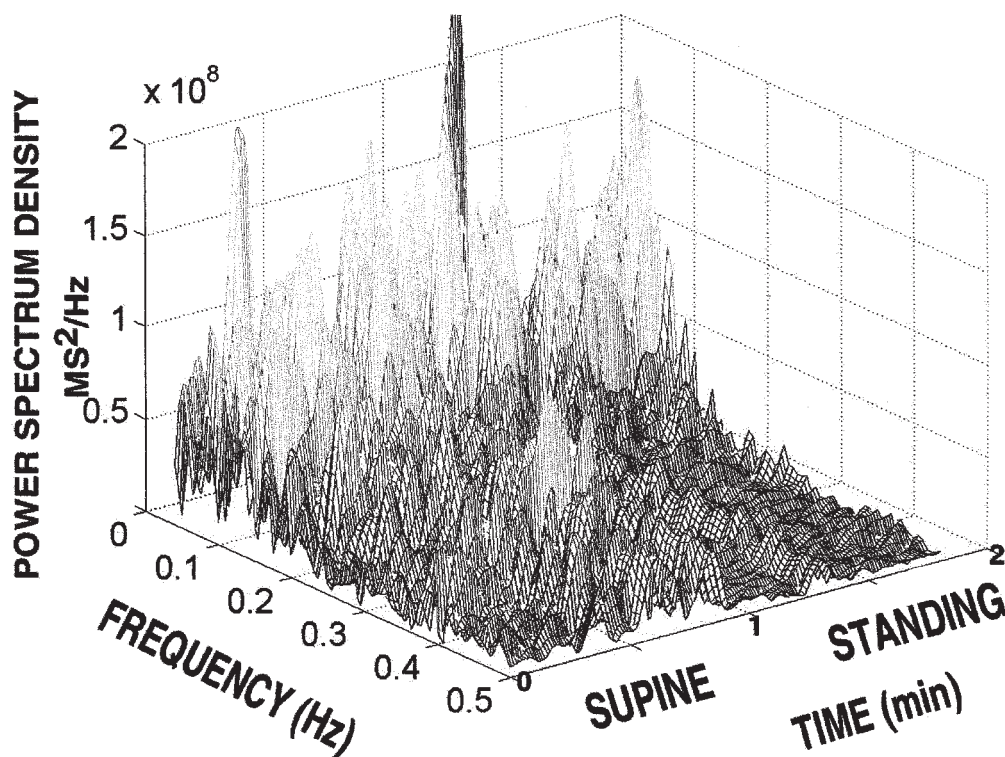


Figure 2. Power spectrum density analysis of HRV in healthy controls supine and standing.

Table 2. Individual differences in power spectral analysis (standing value minus supine value) in 19 male patients with FM and 19 age and sex matched controls.

Frequency domain	Delta* (Standing value – supine value)		p T Test for Independent Variables
	Male FM Patients (n = 19)	Matched Control (n = 19)	
Power (normalized units)			
LF, %	0.734 ± 3.03	12.6 ± 16.2	< 0.0045
HF, %	–0.734 ± 3.03	–12.6 ± 16.2	< 0.0045
LF/HF			
(The mean of individual ratios)	4.46 ± 15.2	11.8 ± 16.3	NS
Heart rate (bpm)	2.4 ± 10.45	11.76 ± 16.3	< 0.0125
R–R interval (ms)	0.004 ± 0.11	–0.12 ± 0.22	< 0.03

*Mean and SD of the individual differences, standing value minus supine value.

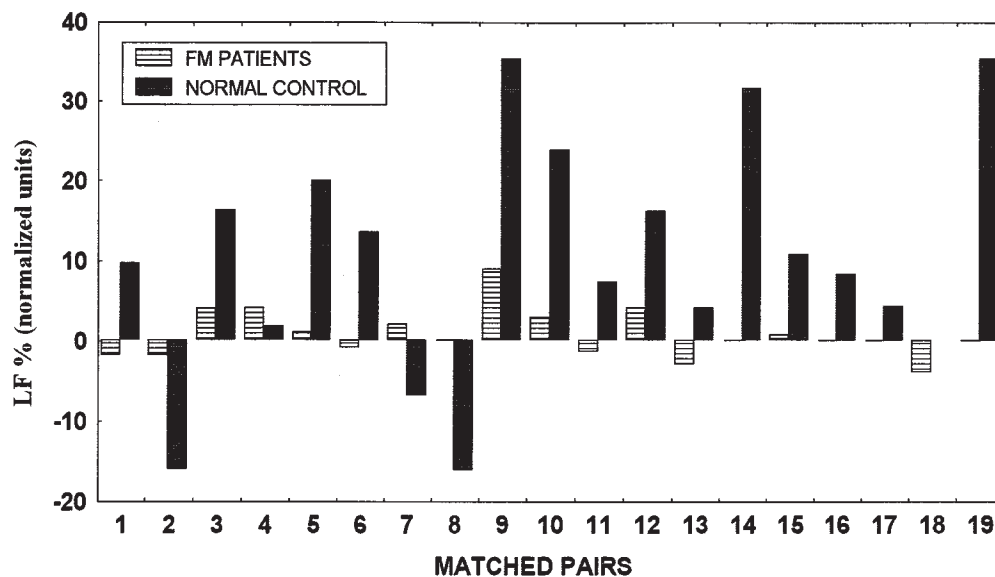


Figure 3. Individual difference in LF component power (standing value minus supine value) of 19 male patients with FM and 19 age and sex matched controls.

the sympathetic autonomic system at rest could be related, in part, to the pathophysiology of symptoms such as fatigue, sleep disturbances, paresthesias, and irritable bowel syndrome. The abnormal autonomic response to sympathetic challenges could explain findings such as low muscle tissue oxygen³⁴, abnormal muscle phosphate metabolism³⁵, decreased threshold for pain, and increased fatigue³⁶ in patients with FM.

This phenomenon appears to reflect a dysfunction of autonomic neuroregulation, as proposed by Martinez-Lavin, *et al*¹¹, who assessed the sympathetic–parasympathetic balance in women with FM and its response to orthostatic stress, by PSA of HRV. The authors showed that in these patients there is a deranged sympathetic response to ortho-

static stress compared to control subjects. While controls displayed an increased power spectral density upon standing ($+0.081 \pm 0.217$ Hz), the FM patients had a discordant response (-0.057 ± 0.097 Hz) ($p = 0.018$). It was suggested that in patients with FM the expected sympathetic surge in response to orthostatic stress is impaired. The authors also observed that the sympathetic component is markedly increased in supine patients with FM, compared to controls in the same posture. Following orthostatic stress this component is decreased in FM patients, while the heart rate itself is increased.

Martinez-Lavin, *et al*³⁷ reported that patients with FM have diminished 24 hour HRV due to an increased nocturnal predominance of LF band oscillations consistent with an

exaggerated sympathetic modulation of the sinus node. Qiao, *et al*³⁸ measured electrodermal and microcirculatory variables at baseline and after acoustic stimulation or cold pressor tests, extending the observation of a decreased sympathetic response to diverse stimuli. Vaeroy, *et al*³⁹ reported that auditory stimulation and cold pressor tests elicited diminished vasoconstrictor response in patients with FM compared to controls. Elam, *et al*⁴⁰ recorded muscle sympathetic activity with microneurography (direct measurement of sympathetic activity from the peroneal nerve) and found less pronounced activation during isometric muscle contraction in patients with FM.

Experimental and clinical studies show that cardiovascular autonomic regulation plays an important role in cardiac morbidity and mortality⁴¹⁻⁴⁵. Studies indicate that decreased vagal activity, defined in terms of low HRV and low HF, is associated with a variety of disease states and increased risk of mortality, including sudden cardiac death^{41,42}. Apart from possible contributions to our understanding of altered autonomic nervous system functioning in FM, PSA of HRV may yield important insights concerning cardiovascular morbidity in this condition. Various cardiovascular diseases⁴³ and mental disorders have been shown to be associated with alterations in autonomic nervous system function. Subjects with dual diagnoses may be at increased risk owing to increased autonomic nervous system involvement^{44,45}. In light of evidence that mortality is increased in patients with FM⁴⁶, and since changes in HRV are also predictive risk factors for cardiovascular morbidity and mortality, followup studies are necessary to determine the course and effect of autonomic dysregulation in patients with FM.

Anxiety and depression. Our study also shows that patients with FM had higher mean scores of depression and anxiety

than controls. Symptoms of depression and anxiety are often found in patients with FM⁴⁷⁻⁴⁹, with an estimated lifetime prevalence of depression ranging from 20 to 83% in clinical studies⁵⁰⁻⁵².

Since autonomic dysregulation has also been found in HRV studies of panic disorder^{53,54}, generalized anxiety disorder⁵⁵, depression⁵⁶, and posttraumatic stress disorder^{57,58}, it is possible that these findings are characteristic of anxiety disorders and/or depression in general, and are not specific to FM. Our findings may reflect a nonspecific anxiety related response pattern in patients with FM. It is also possible that the various clinical syndromes have common underlying pathophysiologic disturbances. A study of the prevalence of posttraumatic stress disorder in patients with FM is in progress.

Is there a sex related difference in autonomic modulation of HRV in patients with FM? Numerous examples illustrate that the rates of certain illnesses differ between men and women (presumably based on biologic differences), reflecting important aspects of the underlying pathophysiology; knowing that FM affects women more frequently than men², we investigated whether the autonomic dysfunction in men is similar to that of women. We compared these data of the male patients with FM with data from a female sample with FM (Cohen H, unpublished data) (Table 3). Both studies took place under similar conditions and were matched for age and smoking.

Caution is required in interpreting the results because previous studies observed sex related differences in HR variability in healthy subjects^{59,60}. Sinnreich, *et al*⁶⁰ showed that men had a 34% higher very low frequency and low frequency power and a higher ratio of low to high frequency power than women.

Our results support findings of other groups that there are

Table 3. Power spectral analysis in male FM patients vs female FM patients. Differences in continuous variables between the women and men were assessed by Mann-Whitney 2 sample test. Categorical variables were compared by chi-square test.

	Male Patients (n = 19) Supine	Male Control Group (n = 19) Supine	Female Patients* (n = 19) Supine	Female Control Group* (n = 19) Supine
Frequency domain				
Power (normalized units)				
LF, % ¹	91.8 ± 3.6	77.3 ± 12.5	87.1 ± 6.4	58.2 ± 23.9
HF, % ²	8.2 ± 3.6	22.6 ± 12.5	12.9 ± 6.4	41.8 ± 23.9
LF/HF ³	13.6 ± 6.3	4.8 ± 3.1	8.8 ± 4.9	2.2 ± 1.7
(The mean of individual ratios)				
Heart rate (bpm) ⁴	82.75 ± 8.6	64.7 ± 7.9	84.3 ± 9.7	69.0 ± 7.4
R-R interval (ms) ⁵	0.73 ± 0.085	0.943 ± 0.14	0.711 ± 0.048	0.78 ± 0.01

Results are expressed as mean and SD.

*Unpublished data.

sex related differences in HRV variables in healthy subjects. Because of these differences in controls, we measured the variations of the modification between the FM groups (male and female) and their respective control groups when age and HR were adjusted. The differences in continuous variables between women and men were assessed by the Mann-Whitney 2 sample test (Table 3). Significant differences between the results of the healthy subjects and women and men with FM, respectively, were taken into account by means of ANCOVA after logarithmic transformation of the data that were not normally distributed (Table 4, Figure 4).

Our results show that women with FM exhibit more

augmented sympathetic activity and reduced vagal tone than men with FM, reflecting a more severe autonomic dysfunction in women than in men with FM. We conclude that sex differences must be considered in studies of cardiac autonomic modulation and HRV.

If a specific dysfunction in the autonomic nervous system in female subjects can be identified, this will provide powerful information to clarify the pathophysiology of those conditions where sex makes a difference.

These findings reveal a new aspect of autonomic dysfunction in men with FM. They indicate that male patients with FM at rest are characterized by a sympathetic

Table 4. Individual differences in power spectral analysis (FM patients' values minus matched control values) in patients with FM.

	Delta* (FM patients' values — matched control values)		p T Test for Independent Variables
	Male FM Patients (n = 19)	Female FM Patients (n = 19)	
Frequency domain			
Power (normalized units)			
LF, %	14.1 ± 12.7	36.8 ± 23.96	< 0.0045
HF, %	-14.1 ± 12.7	-36.8 ± 23.96	< 0.0045
LF/HF	8.54 ± 4.8	7.8 ± 4.9	NS
(The mean of individual ratios)			
Heart rate (bpm)	15.7 ± 12.1	15.76 ± 16.3	NS
R-R interval (ms)	-0.2 ± 0.16	-0.15 ± 0.11	NS

*Mean and SD of the individual differences, standing values minus supine values.

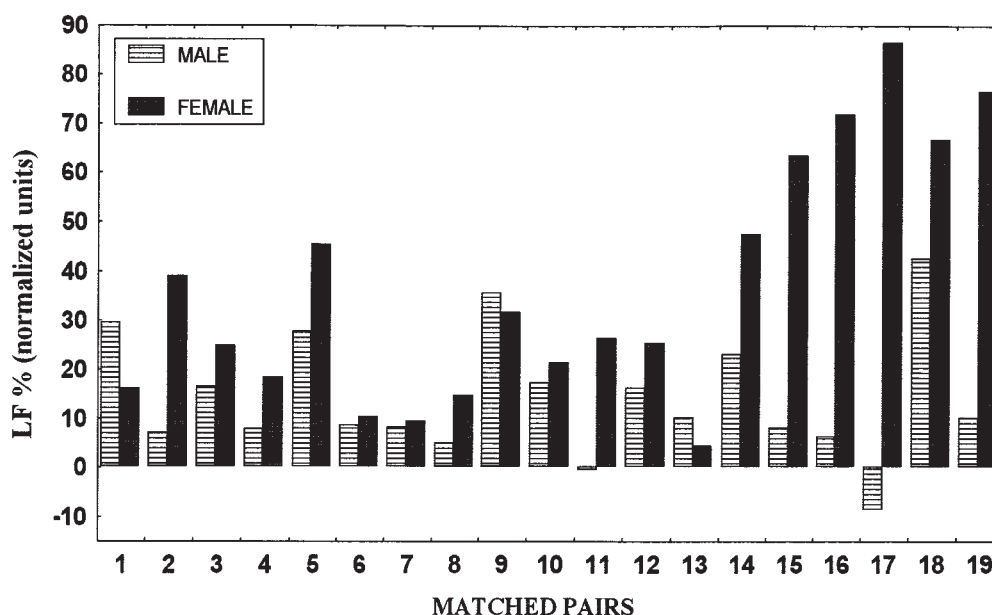


Figure 4. Individual difference in LF component power (FM patients' values minus matched control values) of 19 men with FM and 19 women with FM.

hyperactivity and concomitantly reduced parasympathetic activity. During postural change, men with FM demonstrated an abnormal sympathovagal response.

Since changes in HRV are also predictive risk factors for cardiovascular morbidity, followup studies are necessary to determine the course and effect of autonomic dysregulation in patients with FM.

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