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ORIGINAL ARTICLE

Autonomic changes in fibromyalgia: Clinical and electrophysiological study

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Abstract *Background:* Autonomic nervous system (ANS) dysfunction is one of the suggested pathophysiological mechanisms of fibromyalgia (FM). Its dysfunction may contribute to enhanced pain and other clinical problems associated with FM. Previous studies showed conflicting results regarding ANS function in FM. Some studies showed increased while others showed decreased ANS activity in FM patients. Thus, the autonomic responses in FM patients need further elaboration.

Aim of the work: The aim of this work was to evaluate the autonomic dysfunction in FM patients clinically and electrophysiologically.

Subjects and methods: Twenty-five patients (23 females and 2 males) diagnosed as FM and 15 apparently healthy individuals served as a control group were included in this study. Patients were subjected to thorough clinical examination and assessment of 1 – pain by McGill pain questionnaire (MPQ), 2 – sleep by Visual Analogue Scale (VAS), 3 – depression by Hamilton Rating Scale for Depression (HRSD) and 4 – functional status by Fibromyalgia impact questionnaire (FIQ). Assessment of ANS function was carried out by tilt table test, measuring supine and standing blood pressure (BP) and heart rate (HR) and sympathetic skin response (SSR) of the hands.

Results: Compared to controls, there was a statistically significant decrease of standing systolic BP standing, diastolic BP and standing HR as well as a statistically significant increase in latency and decrease in amplitude of SSR of the hands of the FM patients. HRSD was correlated positively with

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supine systolic BP and standing diastolic BP while McGill pain questionnaire was correlated positively with supine systolic BP. Moreover, VAS falling asleep was correlated positively with standing systolic BP. *Conclusion:* The studied FM patients showed ANS dysfunction in the form of abnormal responses to active and passive changes in posture as well as abnormal SSR.

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1. Introduction

Fibromyalgia (FM) is characterized by chronic widespread pain and also allodynia, a heightened and painful response to pressure.¹ However, FM symptoms are not restricted to pain and other core symptoms including debilitating fatigue, sleep disturbance, and joint stiffness are reported as well.² Some patients may also report difficulty in swallowing,³ bowel and bladder abnormalities,⁴ numbness and tingling⁵ and cognitive dysfunction.⁶ The pathophysiology of FM involves a number of factors, including abnormalities in the neuroendocrine and autonomic nervous systems, genetic factors, psychosocial variables and environmental stressors that interact to amplify pain.^{7,8} Evidence accumulating through years showed that autonomic dysfunction is common in FM.^{9–15} Some of the FM symptoms like sleep disturbances, fatigue, orthostatic intolerance and excessive rate of syncope were attributed to autonomic dysfunction in FM patients.^{14,16,17} Autonomic nervous system (ANS) abnormalities may contribute to enhanced pain and other clinical problems associated with FM via the alteration of physiologic responses required for effective stress management.⁷ It has been suggested that, due to a ceiling effect, the hyperactive sympathetic nervous system (SNS) of such patients becomes unable to further respond to different stressors (sympathetic hyperactivity with hyporeactivity). This explains the constant fatigue, morning stiffness, sleep disorders, anxiety, decreased threshold for pain, pseudo-Raynaud's phenomenon, sicca symptoms and intestinal irritability that these patients suffer from.^{18,19} The function of the ANS is difficult to evaluate in clinical practice. Changes in breathing pattern, presence of mental stress, or even change of posture, alter immediately and completely the sympathetic/parasympathetic balance.²⁰ Accordingly, assessment of ANS under these dynamic conditions will reflect to a great extent the body response in similar real life situations. Noninvasive tests of autonomic function are relatively easy to implement, but can be difficult to interpret.²¹ Among the tools that can be used in this respect are active orthostatic stress test,²² heart rate variability analysis,²³ tilt table test²⁴ and sympathetic skin response.²⁵ Increased sympathetic and decreased parasympathetic activities were detected in FM patients^{26–28} which are related to heart rate (HR) variability¹⁴ and increased blood pressure (BP),¹⁶ suggesting exaggerated autonomic activity. However, other studies reported decreased BP¹³ and reduced HR variability,¹¹ suggesting a hypoactive ANS. Moreover, SSR study showed variable results in FM patients.^{29–31} Thus, based on these conflicting data, the autonomic responses in FM patients need further elaboration.

Aim: The aim of this work was to evaluate the autonomic dysfunction in FM patients clinically and electrophysiologically.

2. Methods

The study included 25 patients diagnosed as FM syndrome according to the American College of Rheumatology criteria (ACR)¹ selected from those attending the Physical Medicine, Rheumatology & Rehabilitation Department, Faculty of Medicine, Alexandria University. Patients with rheumatologic diseases (as rheumatoid arthritis, osteoarthritis, spondyloarthropathy, systemic lupus erythematosus, etc.), vascular diseases, endocrine or metabolic diseases and neurologic or neuromuscular diseases were excluded. Fifteen apparently healthy individuals served as a control group for the autonomic tests and electrophysiological study. The study was explained to the participants and an informed consent was given by each one. The study was approved by the local ethics committee.

2.1. Every patient was subjected to the following

- Detailed history taking (demographic data, history of present condition, past history, family history and menstrual history from female patients).
- General examination with stress on musculoskeletal examination (including tender points) and complete neurological examination.
- Assessment of the clinical manifestations of FM by:
 1. McGill pain questionnaire (MPQ)^{32,33} for pain severity assessment.
 2. Analogical Visual Scale for Sleep evaluation (VAS).³⁴
 3. Hamilton Rating Scale for Depression (HRSD)³⁵ for depression assessment.
 4. Fibromyalgia impact questionnaire (FIQ)³⁶ for functional assessment.
- Assessment of autonomic nervous system in FM by:
 1. Measuring supine and standing blood pressure (BP) and heart rate (HR), i.e. active orthostatic stress test. Sustained drops in systolic blood pressure (> 20 mmHg) or diastolic blood pressure (> 10 mmHg) after standing for 3 min that are not associated with an increase in the pulse rate > 30 beats per minute suggest autonomic deficit.²⁰
 2. Tilt table test, i.e. passive orthostatic test: At first subjects lied supine for 30 min and HR and BP were determined. Then the subject was tilted upright for 30–45 min at an angle of 60–80°. There are two types of abnormal responses. One such response is orthostatic hypotension, defined as a reduction of systolic blood

pressure of at least 20 mmHg or a reduction of diastolic blood pressure of at least 10 mmHg. This hypotension may induce syncope. The other type of abnormal response is postural orthostatic tachycardia, which consists of a sustained increase of heart rate of at least 30 beats per minute or a sustained pulse rate of 120 beats per minute.²⁴

3. Sympathetic skin response (SSR)³⁷: one hand testing was performed for every patient as a measure for sympathetic function using NIHON KOHDEN (Neuro-pack) electrophysiological apparatus.

3. Statistical analysis

Data were analyzed using SPSS software package version 18.0 (SPSS, Chicago, IL, USA). Quantitative data were expressed using range, mean, standard deviation and median, while qualitative data were expressed in frequency and percent. Quantitative data were analyzed using Student's *t*-test to compare between the two groups. Pearson coefficient was used to analyze the correlation between any two quantitative variables. *P* value was assumed to be significant at 0.05 or less.³⁸

4. Results

Twenty-five patients fulfilling the ACR criteria for the diagnosis of fibromyalgia were enrolled in this study. Their median age was 37 years (ranging from 20 to 60). The control group consisted of 15 apparently healthy individuals, their median age was 33 years (ranging from 22 to 56). Only two patients (8%) were males and the majority 23 patients (92%) were females. The control group consisted of 3 males (20%) and 12 females (80%). There were no statistically significant differences between both groups regarding age and gender ($p = 0.328$ and 0.345 , respectively). Fifteen patients (60%) were married, 7 patients (28%) were single, 2 patients (8%) were divorced and 1 patient (4%) was a widow. Thirteen patients (52%) had light work, 10 patients (40%) had heavy work and 2 patients (8%) had no work. The median duration of symptoms was 24 months (ranging from 6 to 84 months).

All patients had pain in the form of deep muscular aching, throbbing, shooting, stabbing or intense burning pain, whereas 20 patients (80%) had fatigue. Eighteen patients (72%) had normal bowel habits, while 7 patients (28%) had irregular bowel habits. All patients had irregular sleep pattern in the form of difficulty in going to sleep, waking up several times during sleep, little amount of sleep and waking up tired.

Assessment of pain severity by MPQ revealed that the median score of the total pain rating index (T-PRI) was 9 (ranging from 6 to 19) and that of the presenting pain intensity-visual analogue scale (PPI-VAS) was 5 (ranging from 3 to 7), while the median score of the overall intensity of total pain experience was 2 (ranging from 2 to 3). Furthermore, assessment of sleep by VAS showed that the median score of the time it took the patient to fall asleep was 40 min (ranging from 30 to 60 min) and that of the amount of sleep the patient slept was 50 min (ranging from 40 to 80 min) whereas the median score of the quality of sleep of the patient was 50 (ranging from 30 to 60).

The median score of depression assessment of the studied FM patient by HRSD was 19 (ranging from 12 to 48). Sixteen

patients (64%) had mild, 5 patients (20%) had severe, and 4 patients (16%) had moderate depression.

On the other hand, the median score of FIQ was 49.40 (ranging from 44 to 70). Thirteen patients (52%) showed mild affliction, 12 patients (48%) showed moderate affliction and none of them had severe affliction.

4.1. Assessment of autonomic dysfunction

Table 1 shows the cutoff points of supine and standing systolic BP, diastolic BP, HR as well as SSR latency and amplitude of the controls.

Table 2 shows comparison between patients and controls regarding the assessment of clinical autonomic dysfunction of fibromyalgia. There was a statistically significant decrease of standing systolic BP, diastolic BP, standing heart rate in FM patients.

Fifteen patients showed decrease in standing systolic BP. Five patients showed decrease in standing diastolic BP, 10 patients (40%) showed decrease in standing heart rate compared to the control group.

Tilt table test was positive (abnormal response in the form of orthostatic hypotension which may induce syncope and postural orthostatic tachycardia) in 16 patients (64%) and negative (normal response in the form of increased heart rate of 10–15 beat/min) in 9 patients (36%). All controls had negative test.

Table 3 shows the results of SSR. There was a statistically significant increase in latency and decrease in amplitude of SSR of the hands of the patients compared to control ($p = 0.001$).

On descriptive analysis, 12 patients (48%) had prolonged latency, 7 patients (28%) had normal latency and 1 patient (4%) had short latency. Moreover, 15 patients (60%) had low amplitude and 5 patients (20%) had normal amplitude. In addition, there were 5 patients (20%) showing unobtainable response.

Table 4 shows that MPQ was correlated negatively with sleep VAS and positively with HRSD and FIQ, while FIQ was correlated positively with HRSD.

On the other hand, different autonomic signs were correlated positively with each other, Table 5.

In Table 5, correlation between different FM questionnaires and autonomic signs shows that HRSD was correlated

Table 1 The determined cutoff points of the studied autonomic variables of the control group.

Parameters	Upper limit	Lower limit
Supine systolic BP (mmHg)	142.45	87.21
Supine diastolic BP (mmHg)	93.87	55.47
Supine HR (beat/min)	79.63	63.83
Standing systolic BP (mmHg)	131.05	76.29
Standing diastolic BP (mmHg)	83.82	50.18
Standing HR (beat/min)	102.47	75.39
SSR		
Latency (s)	1.81	0.85
Amplitude (μ V)	142	41.22

BP: blood pressure, HR: heart rate, SSR: sympathetic skin response.

Table 2 Comparison between patients and controls regarding the assessment of autonomic dysfunction of fibromyalgia.

Parameters	Patients		Controls		<i>t</i>	<i>p</i>
Supine systolic BP (mmHg)						
Range	90.0–140.0		90.0–140.0		0.262	0.795
Mean ± SD	114.20 ± 13.04		115.33 ± 13.56			
Median	110.00		110.00			
Supine diastolic BP (mmHg)						
Range	60.0–90.0		60.0–90.0		0.023	0.982
Mean ± SD	74.60 ± 8.89		74.67 ± 9.15			
Median	80.00		70.00			
Supine HR (beat/min)						
Range	63.0–85.0		66.0–77.0		0.673	0.505
Mean ± SD	70.52 ± 6.25		71.73 ± 3.95			
Median	70.00		70.00			
Standing systolic BP (mmHg)						
Range	60.0–130.0		70.0–120.0		2.366*	0.023
Mean ± SD	92.40 ± 15.078		103.67 ± 13.69			
Median	90.00		100.00			
Standing diastolic BP (mmHg)						
Range	50.0–70.0		50.0–80.0		2.648*	0.012
Mean ± SD	60.0 ± 7.90		67.0 ± 8.41			
Median	60.00		65.00			
Standing HR (beat/min)						
Range	68.0–90.0		80.0–100.0		4.211*	0.001
Mean ± SD	78.80 ± 7.70		88.93 ± 6.77			
Median	77.00		90.00			
Tilt table test	Number	%	Number	%		
Negative	9	36.0	15	100	–	–
Positive	16	64.0	0	0.0		

BP: blood pressure, HR: heart rate, SSR: sympathetic skin response.

* *p* is significant at 0.05 or less.

positively with supine systolic BP and standing diastolic BP while McGill pain questionnaire was correlated positively with supine systolic BP. Moreover, VAS falling asleep was correlated positively with standing systolic blood pressure and VAS sleep quality was correlated positively with tender points count ($r = -0.467$, $p = 0.019$).

Among the different parameters, SSR amplitude showed significant negative correlation with MPQ ($r = -0.403$, $p = 0.046$) and HRSD ($r = -0.428$, $p = 0.033$).

5. Discussion

The current study was carried out to evaluate the autonomic changes in FM patients and their relationship to the clinical presentation of such patients.

Clinical assessment of the studied FM patients demonstrated that the wide spread pain is a cardinal and constant feature of the disease in all patients as assessed by the MPQ. These findings were in agreement with those of Russel³⁹ and others.^{40,41} Moreover, all the studied patients had abnormal sleep pattern which was in agreement with Roizenblatt et al.⁴² and Blotmann et al.⁴³ In addition, most of our patients (64%) exhibited features of mild depression as assessed by HRSD. High prevalence of depressive disorders in FM was also demonstrated by Fietta et al.⁴⁴ Accordingly, it was not surprising that our patients had mild-moderate affliction

Table 3 Comparison between patients and controls regarding the SSR of the hands.

SSR	Patients (25 hands)	Controls (15 hands)	<i>t</i>	<i>p</i>
Latency (s)				
Range	0.50–3.63	1.0–1.98	3.929*	0.001
Mean ± SD	2.21 ± 0.96	1.33 ± 0.24		
Median	2.31	1.29		
Amplitude (µV)				
Range	0.0–110.0	60.0–132.0	6.466*	0.001
Mean ± SD	28.31 ± 32.62	92.0 ± 25.39		
Median	20.00	89.00		

SSR: sympathetic skin response.

* *p* is significant at 0.05 or less.

regarding the impact of FM on their quality of life as assessed by FIQ.

Although FM etiopathogenesis is likely multifactorial, there is no consensus about which mechanisms underlie the diverse symptoms of FM.^{44,45} However, it was suggested that dysregulation of ANS, specifically an overactive SNS is important in FM.^{46,47}

In the present study, assessment of both sympathetic and parasympathetic nervous systems was carried out. The former

Table 4 Correlation between the different questionnaires.

Parameters	<i>r</i>	<i>p</i>
MPQ T PRI		
• VAS sleep amount	-0.486*	0.014
• HRSD	0.693*	0.001
• FIQ	0.546*	0.005
MPQ PPI-VAS		
• HRSD	0.483*	0.014
MPQ overall pain intensity		
• HRSD	0.520*	0.008
VAS amount of sleep		
• HRSD	-0.449*	0.024
HDRS		
• FIQ	0.789*	0.001

MPQ T PRI: McGill pain questionnaire – total pain rating index, MPQ PPI-VAS: McGill pain questionnaire present pain intensity-visual analogue scale, HRSD: Hamilton Rating Scale for Depression, FIQ: fibromyalgia impact questionnaire.

* *p* is significant at 0.05 or less.

Table 5 Correlation between autonomic signs and different questionnaires.

Parameters	<i>r</i>	<i>p</i>
Supine systolic BP		
• MPQ overall pain intensity	0.406*	0.044
• HDRS	0.422*	0.036
Standing systolic BP		
• VAS falling sleep	0.413*	0.040
Standing diastolic BP		
• HDRS	0.429*	0.032

BP: blood pressure, MPQ: McGill pain questionnaire, VAS: visual analogue scale, HRSD: Hamilton Rating Scale for Depression.

* *p* is significant at 0.05 or less.

was predominantly assessed by determining the blood pressure (BP) response to change in posture and by SSR and the latter was assessed by heart rate (HR) variability with the change in posture.⁴⁸ The change in posture (orthostatic test) was active (when standing from supine is actively assumed) and passive (by tilting using a tilt table).^{22,48}

Blood pressure normally changes only slightly on standing from a sitting or supine position. The response to standing is mediated by sympathetic nerve fibers. A response is considered abnormal when the diastolic blood pressure decreases more than 10 mmHg or the systolic blood pressure falls by 30 mmHg within 2 min after standing.⁴⁹ If reflex pathways are defective, blood pressure falls markedly with hemodynamic pooling. In tilt table testing, an abnormal response is defined similarly to that associated with active standing.⁵⁰ Active orthostatic stress is believed to be better than the passive tilting test to trigger vagus-mediated reflexes.²² However, passive head-up tilting provides a more precise level of standardization to the orthostatic stimulus and reduces the muscular contraction of the legs, which can reduce lower-leg pooling of blood.⁵⁰

In the present study, results of active orthostasis revealed a statistically significant decrease in standing systolic and diastolic blood pressure and a significant decrease in standing

heart rate in FM patients. These findings denote normal resting (supine) autonomic function which changed during active orthostasis where our patients exhibited SNS dysfunction as manifested by the BP changes and failure of suppression of the vagal influence on heart rate. Moreover, parasympathetic (PSNS) dysfunction, as indicated by bradycardia, can not be excluded. This was in agreement partially with a Martinez-Lavin et al., study,¹¹ They found the derangement of sympathetic response in 19 FM patients which is markedly increased in supine as compared to normal controls in the same posture (unlike our results). Following an active orthostatic stress this component is decreased in FM patients (like ours) while the heart rate itself is increased (unlike ours).¹¹ Keleman et al.¹² also described a similar study with comparable results to Martinez-Lavin et al.¹¹ while Cohen et al.⁵¹ reported that the patients with FM at rest are characterized by sympathetic hyperactivity and concomitantly reduced parasympathetic activity. During postural changes, patients demonstrated an abnormal sympathovagal response. This was also in agreement with the results of orthostatic test performed by Doğru et al.⁸ They detected decreased parasympathetic and increased sympathetic activities during orthostatic stress (stand and supine tests) in FM patients.

Moreover, in the current study, 16 patients (64%) were positive in tilt table test. This was in agreement with Bou-Holaigah et al.¹³ Also, Naschitz et al.⁵² found that cardiovascular response to upright tilt table test was significantly different in FM patient. In another study performed by Furlan et al.,¹⁶ the effect of head-up tilt table test and muscular sympathetic nerve activity was evaluated in FM patients. They concluded that patients with FM have an overall enhancement of cardiovascular sympathetic activity during recumbency (unlike our results). The lack of increased sympathetic discharge to vessels and decreased cardiac vagal activity characterizes their autonomic profile during tilt test, and might account for the excessive rate of syncope.¹⁶

Accordingly, the pre-mentioned studies demonstrated ANS dysregulation in FM manifested by basal (at rest) sympathetic hyperactivity and concomitantly reduced parasympathetic activity (unlike our results). Not only at rest but also there is an abnormal autonomic response to different stressors including postural changes (similar to our results). The abnormal sympathovagal response to postural changes in FM patients indicates that the activation of one or more groups of arterial or cardiopulmonary baroreceptors may be impaired and thus contribute to the inadequate response.¹³ Another proposed explanation for the abnormal postural responses of FM patients to postural changes is attributed to the basic physiological principle that chronic hyper-stimulation of the beta-adrenergic receptors at rest leads to receptor desensitization and down-regulation preventing further response in stressful situations.²⁰ The latter explanation can not fit with our study because our results showed that FM patients had normal autonomic activity at rest. The difference between our results and others may be related to the difference in the methodology used to assess autonomic dysfunction.

In the present study there was a statistically significant increase in SSR latency of patients and a statistically significant decrease in SSR amplitude of patients. Our results agreed partially with those of Ulas et al.,⁵³ who found that the latencies of SSR recorded from both palms and soles of 34 female FM patients were significantly longer than the healthy subjects.

Moreover, Unlu et al.²⁹ investigated the autonomic dysfunction in FMS by recording SSR from palmar, plantar and genital regions in 28 FM married female patients and 18 married healthy females. They found that the amplitude of SSR recorded from palmar, plantar and genital regions was lower than in the control subjects.²⁹ In contrast to our results, Çakir et al.,³⁰ observed a statistically significant decrease in distal latency, and a statistically significant increase in amplitude of SSR in FM patients suggestive of sympathetic overactivity. Ozgocmen et al.,³¹ studied SSR in 29 female patients with FM and 22 healthy age-matched female controls. SSR latencies of patients' hands and feet had no significant difference compared to the controls.³¹ The controversial results in the literature regarding SSR whether decreased, increased or normal may support the notion that here is a great variability of SSR reproducibility among normal individuals.⁵⁴ However, based on the results of the different studies, it can be assumed that involvement of the sympathetic cholinergic system is not as frequent and consistent as that of the adrenergic system. In our study, both systems are significantly affected in FM patients. The abnormal SSR latency in our study can be attributed to the presence of a neuropathy affecting unmyelinated/poorly myelinated fibers more than a cholinergic dysfunction in the transmission between the nervous output and the sweat glands as the efferent unmyelinated fibers accounting for most of the latency, although a slow conduction in the afferent branch of the reflex arc, or central delay in the activation of sympathetic neurons, may cause relevant changes. Moreover, the amplitude of response is highly variable and its decrease is related to a decreased sympathetic outflow. However, the main clinical consideration remains the presence/absence of the response.⁵⁵

In the present study, MPQ was negatively correlated with VAS of sleep amount. This was in agreement with a study performed by Roizenblatt et al.,⁴² where sleep quality was significantly lower in patients with FM than in controls and patients reported worsening of pain symptoms after poor sleep.⁴² Moreover, a large epidemiologic study supports the correlation between sleep and pain.⁵⁶ The negative correlation between the number of tender points and the VAS sleep quality in the present study denotes that with increasing number of tender points sleep quality becomes worse. Disturbed sleep may contribute to enhanced pain because it was found that the abnormal EEG pattern during sleep was associated with the reduced production of growth hormone and IGF-1 which are necessary for the repair of muscle microtrauma. Thus, sleep disturbances may impair the healing of muscle tissue damage and enhance the perception of muscle pain.⁵⁷

Moreover, in the present study, FIQ was positively correlated with MPQ and HRSD (excessive pain and depression were associated with poor quality of life of the FM patients) and MPQ was also positively correlated with HRSD. In one study, it was found that the symptoms and the resulting disability of FM are strongly related to the feelings of anxiety and apprehension regarding the nature and prognosis of the condition ('illness worry'), to a greater extent than in RA.⁵⁸ Although most of the studies showed a significant adverse effect of anxiety on the quality of life of FM patients, it is also easy to infer that depression has the same effect as our results.

In the current study, standing systolic and diastolic BP showed positive correlations with VAS falling asleep and HRSD respectively denoting that sympathetic overactivity may affect the sleep pattern and psychological state of the

patient. However, these effects showed some inconsistency with the available literature. Most of the available studies showed adverse effects of ANS dysfunction in FM on sleep.^{14,42,43,59} Most of these studies attributed sleep disturbance in FM patients to the changes in nocturnal autonomic activity and the clinical impact of this autonomic circadian disturbance on FM patients.^{14,42,43,59} On the other hand, most of the studies found an association between ANS dysfunction in FM patients and anxiety (not depression). In one study, diastolic BP and HR were negatively related to stress, pain, and anxiety.⁴⁵ While in another one, it was concluded that anxiety-induced stress is known to evoke the behavioral alerting response in humans, which is associated with an increase in sympathetic activity and a decrease in parasympathetic activity to the heart.^{59,60}

From this study, it can be concluded that FM patients had ANS dysfunction in response to active and passive changes in posture involving both sympathetic (detected by blood pressure changes) and parasympathetic components (detected by heart rate changes), i.e. there is an abnormal sympathovagal response in our FM patients. The cholinergic component of the SNS (detected by SSR abnormalities) was also hypoactive. The ANS dysfunction in the current study manifested predominantly by hypoactive SNS.

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