Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2023 August; 6 (9s): 1165-1174

Autonomic Dysfunction in Patients with Fibromyalgia

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Received: 24- June -2023
Revised: 27- July -2023
Accepted: 21- August -2023

Abstract

Fibromyalgia is considered in the medically unexplained physical symptoms (MUPS) category due to the unclear etiology and pathophysiology of the disease. The aim was to study alterations of autonomic functions in these patients by using heart-based tests, blood pressure (BP)-based tests, and sympathetic skin response (SSR). In this prospective cohort study, patients diagnosed with fibromyalgia (FM) and other healthy subjects were taken in the medical city, Baghdad (Iraq). The case study (n = 47) has been designed to assess the autonomic nervous system functions among patients with fibromyalgia versus healthy individuals. According to the 2010 ACR Fibromyalgia Diagnostic Criteria (Modified 2011), a patient meets the diagnostic criteria for fibromyalgia if the following conditions are met: Widespread Pain Index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3-6 and SS scale score ≥9. The outcomes delineated that the female population in the fibromyalgia group explicated significant increases in DBP differences in comparison to the control group. The heart rate variability parameters, including Valsalva ratio and deep breathing E/I ratio, were significantly different between fibromyalgia patients (the experimental group) and healthy individuals (control group). Similarly, the inferences exposed the statistical correlation among the clinical features of groups and their SSR outcomes in fibromyalgia patients.

Keywords: fibromyalgia, sympathetic skin response, autonomic function tests.

1. Introduction

Fibromyalgia is a syndrome of widespread complaints associated with generalized musculoskeletal pain, fatigue, reduced muscle strength, depressive mood, decreased quality of life, and functional limitation (1). Globally, the prevalence of fibromyalgia (FM) is around 2-4 percent in the general population, with predominantly increased incidences in female individuals(2) .Although the etiology of fibromyalgia is unknown and ambiguous, it is generally considered to be a central sensitization and inappropriate diffuse noxious inhibitory syndrome(3).

The 2010 ACR Fibromyalgia Diagnostic Criteria (Modified 2011) is a method used for diagnosing fibromyalgia. A patient satisfies the diagnostic criteria for fibromyalgia if the following conditions are met: Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3-6 and SS scale score ≥9. Symptoms have been present at a similar level for at least 3 months(4).

FM disrupts the major stress response system, which includes the hypothalamic pituitary-adrenal axis and the autonomic nervous system (ANS)(5). ANS dysfunction appears to play a major role in the pathogenesis of fibromyalgia. Aberrant ANS responses are one biological marker of fibromyalgia and encompass sympathetic hyperactivity and reduced parasympathetic activity(6).

Therefore, patients with fibromyalgia present with blunted sympathetic vascular modulation, impaired cardiac vagal withdrawal to gravitational stress, and consequently reduced orthostatic tolerance(7). Increased adrenergic tone and disrupted sympathetic response to stress could also contribute to other clinical manifestations of FM, including tachycardia, postural intolerance, Raynaud's phenomenon, and intestinal irregularity(8).

Cardiac autonomic dysfunction (CAD) is frequently found in FM patients and may increase the risk of cardiovascular events and mortality(9). Several techniques are routinely used for the assessment of ANS function in individuals with FM, including sympathetic skin response (SSR), heart rate variability (HRV), etc. It is commonly utilized by simple and non-invasive electrophysiological procedures(10).

With this background, the major objectives of the study are discussed below:

- To study the correlation between clinical features and autonomic function test outcomes of fibromyalgia patients by using electrophysiological techniques.
- To explore the significant differences in autonomic nervous system function outcomes between control group and experimental group individuals.

1.1. Paper organization

The organization of the paper were illustrated in the following section. Section I states the introductory concepts of research and objectives of the research. Section II enumerated the material and methods, Section III deliberated the results of research implementation and section IV explicates the conclusive statement of the study.

2. Material and methods

2.1. Patient Enrollment and Study Period

A prospective cohort study was designed to assess the autonomic nervous-system functions among the patients having fibromyalgia versus healthy individuals. 23 patients with fibromyalgia were enrolled in the study, constitute the experimental group (EG), and 24 normal persons were enrolled as a control group (CG) population.

Twenty-three patients diagnosed with fibromyalgia were recruited from outpatient clinic, medical city, Baghdad, Iraq. Constitute the experimental group (EG). All patients were diagnosed with fibromyalgia by a rheumatologist or neurologist and evaluated between January 2021 and December 2021. The sample included 17 women and 6 men their ages ranged from 18 to 61 years and had well established diagnosis of fibromyalgia. Inclusion criteria were: fulfillment of the 2010 American College of Rheumatology (ACR) Fibromyalgia diagnostic criteria (Modified 2011) patient satisfies diagnostic criteria for fibromyalgia if the following conditions are met: Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3-6 and SS scale score ≥9.

Symptoms have been present at a similar level for at least 3 months, lack of co-morbid conditions or medications that could affect ANS function, including any type of sleeping pills, tranquilizers or antidepressants, prior to the study; no evidence of polyneuropathy, myopathy or major depression, congenital cardiac disease, coronary artery disease or cardiomyopathies;

Twenty-four healthy gender and age matched individuals that visited same clinic within the same period composed the control group (CG).

Subjects were instructed to refrain from food, caffeine, tobacco and alcohol for at least 12 hours and vigorous physical activity for at least 24 hours prior to ANS measurement, they were advised to wear comfortable clothes and to shower the night before testing without using anybody lotions, powders, or creams below the neck, also to drink water and stay hydrated All investigations took approximately 20 minutes for each subject excluding a resting period.

Informed consent was obtained from all the participants (both patients and healthy controls) prior to the study.

2.3. Data collection

To evaluate ANS functions, SSR, HR variability (R-R interval variation), and BP changes were measured using Cadwell (USA) 4-channel electromyography equipment. The tests were conducted in a quiet room at room temperature of 22 ± 2°C, and the skin temperature of patients at least 35ºC while performing the test. A surface recording disc electrode is fixed to the left anterior chest area at the fourth and fifth intercostal space and a reference electrode is fixed at the left anterior axillary line over the fifth or sixth rib. The ground electrode is placed on the midline of the sternum. The sensitivity and sweep speed are adjusted to display the QRS complexes on the screen. HR variability analyses are based on the measurement of the time intervals between successive QRS complexes, which reflect the regulation of the HR by the ANS via its sympathetic and parasympathetic control mechanisms**.**

The test battery included the recording of HR responses at rest (normal breathing), deep breathing, Valsalva maneuver, and standing.

The HR response to deep breathing was expressed as deep breathing difference, which was the difference between the maximum HR (shortest RR interval during inspiration) and the minimum HR (longest RR interval during expiration), in patient breathing at six cycles per minute. The exhalation: inspiration (E: I) ratio was obtained using the following formula:

The RR-IV% = (the longest RR – the shortest RR) x 100/mean of RR values(11)

The HR response to the Valsalva maneuver expressed as Valsalva ratio was tested while the patient was in the supine position and the head slightly elevated to about 30°. The patient was asked to strain against 40 mmHg for 15 s by blowing into a mouthpiece attached to a sphygmomanometer. The ratio of the longest RR interval 30-45 s following the release of strain to the shortest RR interval during strain was calculated. The minimal HR occurs at 15-20 s after releasing the strain(12).

HR response to standing was obtained after the patient has been resting at least for 20 min. It is expressed as the 30:15, which is the ratio of the longest RR interval (slowest HR) at 30 s to the shortest RR interval (fastest HR) at 15 s, following an abrupt change in position from supine for 3 minutes to standing by a tilt table(13)

Changes in BP following change of position from supine to standing after 3 minutes were also calculated. The postural decrease in BP after 3 min was taken as the difference between BP (systolic and diastolic BP) lying and the BP (systolic and diastolic BP) standing. A decline in systolic BP by more than 20 mmHg and by more than 10 mmHg for diastolic BP is considered abnormal(12).

When measuring SSR, an active Ag/AgCl disk electrode was placed on the palm, sole, while a reference electrode was placed on the dorsum of the hand, foot respectively. A single electrical stimulus ranged from 12 to 20 mA with a pulse width of 0.1 ms was given unexpectedly to the median, tibial nerves opposite the recorded side**.** To avoid any habituation, the inter-stimulus interval was between 20 and 30 seconds(14).

2.4 Statistical analysis

The data has been assessed by statistical analysis. Exploratory data representation, Independent T sample test, One-way Analysis of Variance (ANOVA) and correlation test performed in the results, Data were fed to system and data analysis proceeded through IBM SPSS software package version-20.0.

The quantitative approach is persuaded to explicate the relationship of autonomic function tests parameters among the fibromyalgia patients. The results are brought down for control and experimental group individually. The significance of gained outcomes were judged at that p value having lesser than 0. 05..

2.5. Ethical considerations

The research was explained to all the participants and informed consent given by everyone. The research to get persuaded has been approved by local ethics-committee

3. Results

In the prospective cohort study, the aim was to evaluate the autonomic function in fibromyalgia patients.

Table 1. Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
SSR foot Onset latency (ms)	Control Group	24	1.52	.282	.058
	Experimental Group	23	2.57	.344	.072
DBP difference in mmHg	Control Group	24	1.15	.442	.090
	Experimental Group	23	1.23	.344	.072
SSR hand Amplitude (µV)	Control Group	24	2.94	1.179	.241
	Experimental Group	23	2.61	1.076	.224

The outcomes of group statistics table which comes under independent sample t test has been depicted in table 1. The test has considered three parameters that include diastolic Bp differences, Sympathetic Skin Response (SSR) amplitude of hand and onset latency of foot parameter.

The corresponding mean value and the standard deviation values in experimental and control groups are listed. From the observation, the highest mean value is 2.61 and 2.54 of experimental group of SSR amplitude of hand and experimental group test values of SSR latency of foot signifies the differences between healthy (control) and fibromyalgia affected patients.

The statistical mean differences are evolved in those patients having fibromyalgia and the healthy individuals. And the mean 1.23 represent the diastolic Bp difference of experimental group denoting the severity of this parameter changes among the fibromyalgia patients.

The highest mean values are depicted for the electrophysiological results of SSR onset latency of foot and SSR amplitude of hand for those individuals present in the experimental group.

Table 2. Independent Samples Test

		Levine's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
	Equal variances assumed	1.074	.305	.514	45	.006	.047	.092	-.138	.232

SSR foot Onset latency (ms)	Equal variances not assumed			.512	42.575	.005	.047	.092	-.139	.233
DBP difference in mmHg	Equal variances assumed	4.549	.038	1.031	45	.030	.120	.116	-.114	.353
	Equal variances not assumed			1.036	43.219	.023	.120	.115	-.113	.352
SSR hand Amp (µV)	Equal variances assumed	.508	.480	-.203	45	.018	-.067	.330	-.731	.597
	Equal variances not assumed			-.204	44.899	.040	-.067	.329	-.730	.596

The independent T-sample test outcomes were depicted in table (2). The outputs deliberated that existence of statistical mean-differences between Control Group and Experimental Group with respect to the results of SSR onset latency of foot, SSR amplitude of hand and differences in Diastolic Bp.

This is affirmed by the significant values 0.006, 0.005, 0.030, 0.023, 0.018 and 0.040 which are comparatively lesser than default p-value (0.05). Since, the obtained values seem lesser than p value (0.05), the mean values of the diastolic Bp difference, SSR onset latency of foot, SSR onset latency of hand for individuals present in two independent groups experimental and control group are said to be statistically significantly different with one another.

The mean variances of the Diastolic Bp difference and SSR responses seems to get vary in the persons having fibromyalgia and the healthy individuals, hence it proves the variations in the Diastolic Bp and SSR responses between experimental group and healthy group individuals .

The paired Sample t-test referred as dependent Sample t-test, a statistical method, for determining if the mean-differences between two observations sets is zero. The effectiveness of an entity or an intervention can be assessed through Paired sample test. The performance/ values of the parameters in two different groups, and to assess the differences accomplished through paired Sample t-test.

Table 3. Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Deep breathing E/I ratio (Control group)	2.34	47	.479	.070
	Deep breathing E/I ratio (Experimental group)	2.1702	47	.63654	.09285

The paired sample statistics, outcomes are delineated in the above table (3). The table provides the univariate descriptive statistics such as mean, size of samples, standard-deviation and standard error for every entered variable.
The non-missing values for all the variables are the use cases. The high mean values are obtained for deep-breathing E/I ratio of individuals in experimental group rather than control group. The mean variations have differences among healthy individuals and fibromyalgia patients.

Table 4. Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	Deep breathing E/I ratio (control group) & Deep breathing E/I ratio (Experimental group)	47	.376	.009

The bi-variate Pearson correlation co-efficient explicates the correlation among the pair of parameters deep breathing E/I in control group and experimental group. The variables are associated with one another for specific individuals.

Table 5. Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Deep breathing E/I ratio (CG) Deep breathing E/I ratio (EG)	.17021	.63654	.09285	-.01668	.35711	1.833	46	.003

The significance value of this test, deliberates the differences in mean values of Deep breathing E/I ratio, of control group and experimental group. The significance of the paired variables Deep breathing E/I ratio differs from that of control group and the experimental group participants as well. This entity Deep breathing ratio is measured resulting in pairs of observations like in control group and experimental group.

Table 6. Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
SSR foot Amp (μV)	Experimental Group	23	2.79	.898	.187
Exp WPI	Experimental Group	23	1.13	.344	.072

Table 6 has listed the outcomes of the group statistics of the independent sample-t test. The test has considered certain parameters such as SSR foot amplitude and WPI values in patients with FM.
The highest mean 2.79 and 1.13 represent the patients who come under the experimental group after intervention were observed to have high medical condition changes with respect to of SSR foot amplitude.

Table 7. Independent Samples Test

		Levine's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
SSR hand amplitude(μV)	Equal variances assumed	1.238	.272	1.102	45	.027	.270	.245	-.223	.763
	Equal variances not assumed			1.099	43.524	.010	.270	.246	-.225	.765
Exp WPI	Equal variances assumed	1.074	.305	-.514	45	.000	-.047	.092	-.232	.138
	Equal variances not assumed			-.512	42.575	.034	-.047	.092	-.233	.139

The independent T-sample outcomes, were delineated in above table 7. The outcomes depict that the existence of statistical mean differences of considered parameters such as SSR hand amplitude and Exp WPI with respect to experimental group have variations, since the significant values of those parameters 0.027, 0.010, 0.000 and 0.034

which are comparatively less than the p value (0.05). This illustrate the statistical mean significance of parameters SSR foot amplitude and WPI, of the experimental groups are said to be statistically significant and proved.

Table 8. Correlations

		DBP difference in mmHg	SSR foot Onset (ms)	Valsalva Ratio
DBP difference in mmHg	Pearson Correlation	1	.168	.062
	Sig. (2-tailed)		.002	.014
	N	47	47	47
SSR foot Onset (ms)	Pearson Correlation	.168	1	.095
	Sig. (2-tailed)	.002		.000
	N	47	47	47
Valsalva Ratio	Pearson Correlation	.062	.095	1
	Sig. (2-tailed)	.014	.000	
	N	47	47	47

The results of the correlation analysis have been reported in the table (8). The analysis has been performed by using tests that include Diastolic Bp difference, SSR onset latency of foot, Valsalva ratio. The Pearson coefficient of the parameters in Diastolic Bp difference and SSR onset latency of foot is 0.168, which signify that there is a positive correlation between the considered parameters that is when Diastolic Bp difference increases, SSR onset latency of foot also increases. The significance value of these two parameters is 0.002 and 0.014 which is comparatively less than the default P value (0.05) proves the positive relationship among the variables. Similarly, the Pearson coefficient of the parameters representing the Valsalva ratio and Diastolic Bp difference is 0.062. This value signify that these parameters are directly proportional to each other. That is, when Valsalva ratio increases, Diastolic Bp difference increases. The significant value of these parameters is 0.014 which is comparatively less than the default P value (0.05). Likewise, the Pearson coefficient value of parameters representing SSR onset latency of foot and Valsalva ratio is 0.095, which denote that when SSR onset latency of foot increases, Valsalva ratio will increase simultaneously. The value of significance for these parameters is 0.040. The overall results of the correlation analysis depict the strong correlation between the values of SSR, Valsalva and Diastolic Bp difference.

Table 9. Correlations

Control Variables			Exp WPI	SSR hand amplitude (μV)
Deep breathing E/I ratio & DBP difference in mmHg	Exp WPI	Correlation	1.000	.119
		Significance (2-tailed)	.	.436
		df	0	43
	SSR hand amplitude (μV)	Correlation	.119	1.000
		Significance (2-tailed)	.436	.
		df	43	0

Partial correlation aids in determining the linear relationship between the two parameters under one or more controlling variable. The Pearson coefficient of the parameters representing WPI and SSR hand Onset is 0.119 which denotes the positive correlation between WPI and SSR hand Onset parameter which controls the variable (controlling effect by) Deep-breathing E/I ratio and DBP difference. Thus, these results illustrate the partial correlation between the considered parameters WPI, SSR hand Onset parameters when controlling for DBP difference and Deep-breathing E/I ratio.

4. Discussion

There are certain other existing researchers who have made attempts to investigate fibromyalgia from different perspectives and with various other medical conditions. One such conventional researcher (15) formulated the research to compare the fibromyalgia patients and healthy controls with various electro diagnostic testing and also attempted to validate if there is any correlation between electro diagnostic measures. The results of the research revealed that the SSR latency was observed to be indifferent between the fibromyalgia patients and healthy individuals. The outcomes revealed that the patient's gender and age did not have significant differences on the electro diagnostic measures.

Similarly, the traditional researcher (16) performed a cross sectional study with the aim of measuring the central sensitization and autonomic activity in fibromyalgia patients when compared with the healthy individuals in the control group. The autonomic activity was measured with heart rate variability, a deep breathing test, and electrodermal activity in three physiological states. The results emphasized that there is no significant difference between fibromyalgia patients and healthy individuals in the control group. In addition, normal parasympathetic activity and varying degrees of sympathetic hyperactivity were observed in fibromyalgia patients.

In parallel to the previous research, conventional work (17) has attempted to estimate the physical fitness and cardiac autonomic activity among female patients with moderate to severe fibromyalgia and healthy female individuals.

Our results are in agreement with previous research (6) that aimed to measure the autonomic nervous system (ANS) dysfunction in patients with fibromyalgia and analyze the correlation of ANS dysfunction with neuropathic pain and severity of disease. The research outcomes determined that those FM patients had ANS dysfunction with minimal sympathetic activity and a rise in the level of sympathetic activity in comparison to the healthy cases (CG). When this sympathetic activity is measured with the amplitude of SSR, its relationship with fibromyalgia is elucidated. The outcomes further stated that this amplitude explicated to have significant high and low SSR latencies while screened with those FM patients.

In line with the above discussion, the outcomes of this study deliberated that the autonomic function tests parameters of the control patients and experimental group patients, such as SSR onset latency of foot, Diastolic Bp difference, and SSR amplitude of hand possess statistical mean differences between those groups. This implies that control group healthy persons and the experimental individuals acquired with fibromyalgia, had difference in the measurement values in SSR, diastolic Bp difference values. The fibromyalgia affected persons shows higher values of those parameters in comparison to healthy persons. This has been evidenced through independent T-sample test.

Similarly, the mean differences of two sets of observations deep breathing E/I ratio in control group and in experimental group are determined using Paired sample test. The correlation among the control group and experimental group individuals for this Deep breathing ratio parameter are explored using paired sample correlation how they are associated with one another, if each person has same increasing ratio or inversely proportional or one is stable.

The means of the parameter between control and experimental group were statistically significantly different with one another, hence proving the variations in the values (Mean=.270, SD=.245) in CG and Mean=-.047, SD=0.092 in experimental group. The mean variances of individuals SSR hand amplitude and Exp WPI are found to be statistically significant, in control group and experimental explicated using independent T-sample test. Similarly, the association among the Diastolic Bp difference in mmHg, SSR onset latency, R-R IV ratios during Valsalva and Deep breathing among control participants and experimental group participants are explored through correlation test.

5. Conclusion

The present study concluded that patients with fibromyalgia showed statistically significant mean differences in SSR hand and foot amplitude along with SSR foot onset latency values as compared to control group. Similarly, the low significance value, implies that population means of the parameters DBP difference, SSR hand amplitude, SBP difference, Deep breathing E/I ratio and SSR hand onset latency of the fibromyalgia patients seems to be statistically different from parameters in healthy individuals, which reveals in the severity scores as well.

Further to this, differences in the DBP, breathing ratio E/I ratio, SSR hand amplitudes, SSR foot onset latency and Exp WPI of control group individuals were statistically significantly different than the experimental group individuals.

Other inferences of study deliberated that significant correlation exists between cardiovascular parameters deep breathing E/I ratio & DBP difference in mmHg to have partial relationship on the Severity scores of FM patients and their SSR hand onset value (SSR responses). The Correlation among the DBP difference, SSR foot Onset and Valsalva Ratio reveals the association among the clinical features of patients and their SSR in fibromyalgia patients by using SSR technique which may help to explore potential associations of them.

6. Declaration

- **Conflict of Interest:** The author reports that there is no conflict of Interest.
- **Funding:** None
- **Acknowledgement:** None

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