



# Relationships of autonomic dysfunction with disease severity and neuropathic pain features in fibromyalgia: is it really a sympathetically maintained neuropathic pain?

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**Background:** The pathophysiology of fibromyalgia (FM) involves many mechanisms including central nervous system sensitization theory, autonomic nervous system (ANS) dysfunction, and recently small fiber neuropathy. While the small fiber neuropathy itself can cause ANS dysfunction and neuropathic pain (NP), it is still unknown whether ANS problems have an association with severity of disease and NP in patients with FM. The aim of this study was to evaluate ANS dysfunction in FM patients and to explore possible associations of ANS dysfunction with disease severity and NP.

**Methods:** Twenty-nine FM patients and 20 healthy controls were included in this cross-sectional study. Participants were tested using sympathetic skin responses (SSR) and R-R interval variation analyses for sympathetic and parasympathetic ANS dysfunction, respectively. Disease severity and somatic symptoms of patients with FM were evaluated using the ACR-2010 scales and Fibromyalgia Impact Questionnaire, and NP symptoms were evaluated using the Pain Detect Questionnaire and Douleur Neuropathique questionnaire.

**Results:** FM patients were found to have ANS dysfunction characterized by increased sympathetic response and decreased parasympathetic response. SSR amplitudes were found to be correlated with a more severe disease. Although non-significant, NP severity tended to be associated with a decrease in sympathetic and parasympathetic activities.

**Conclusions:** ANS dysfunction may play a role in the pathophysiology of FM. The trend of decreased ANS functions in FM patients exhibiting NP contradicts the notion that FM is a sympathetically maintained NP and may be explained with small fiber involvement.

**Key Words:** Autonomic Nervous System; Central Nervous System Sensitization; Fibromyalgia; Neuralgia; Severity of Illness Index; Small Fiber Neuropathy; Surveys and Questionnaire; Sympathetic Nervous System.

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## INTRODUCTION

Fibromyalgia (FM) is a complex syndrome characterized by chronic widespread pain accompanied by various somatic and sensory symptoms without any objectively verifiable pathology. Despite a growing body of research, the etiology of FM remains unclear [1]. Numerous studies, however, have provided insights into the pathophysiology of FM. Most of these studies have provided convincing evidence for central nervous system sensitization that shares some features of neuropathic pain (NP) syndromes [2]. Although the central sensitization phenomenon has become the main theory, many mechanisms have also been proposed and new findings continue to emerge [1]. Evidence accumulating over the years suggests that autonomic nervous system (ANS) dysfunction is common in FM and may play an important role in generation and maintenance of chronic pain and multisystem symptoms [3–5]. However, conflicting results have been obtained regarding the pattern of ANS dysfunction. In most studies, increased sympathetic and decreased parasympathetic activity was observed in FM patients compared to healthy controls [6,7]. Sympathetic dominance in FM was further supported by the findings of linear correlations between indices of sympathetic activity with pain intensity and some of the symptoms of FM [3,8]. Based on the hypothesis of sympathetic overactivity, some authors framed FM as a sympathetically maintained NP syndrome [9]. In contrast to these studies, some other studies have documented a reduced ANS activity in both at the sympathetic and parasympathetic level in patients with FM [10,11]. On the other hand, most recent studies have demonstrated impaired small fiber nerve function in subsets of FM patients, which is congruent with NP symptoms [12–14]. In consequence, much interest has recently been expressed in the possible role of small fiber neuropathy in the neuropathic and autonomic symptoms of FM. Therefore, some authors tend to consider FM as stress-related dysautonomia with NP features [1].

A wide variety of techniques have been used to assess ANS function in patients with FM. Among these, sympathetic skin response (SSR) and heart rate variability (HRV) analyses are commonly used, utilizing simple and non-invasive electrophysiological methods [15]. SSR provides an indirect measure of sympathetic skin outflow to the sudomotor glands in response to internal and external stimuli, and is considered an obtainable index of the function of sympathetic postganglionic fibers [15]. The efferent part of this reflex arch is via thin unmyelinated C fibres, while the afferent part is variable. SSR studies showed conflicted results in FM patients. Some studies have found longer latencies and/or lower amplitudes indicating decreased

sympathetic activity [16] while others have found shorter latencies and higher amplitudes indicating increased sympathetic activity [17] in FM patients comparing to controls. On the other hand, analysis of HRV from ambulatory electrocardiogram (ECG) recordings is the most frequently used technique to determine parasympathetic autonomic dysfunction in FM. HRV is based on the variability of heart rate at rest and in response to deep breathing, orthostatic changes, and different types of maneuvers [18]. Although there are some inconsistencies and the level of evidence is moderate to low, the majority of HRV studies have pointed towards significantly lower HRV in FM patients compared to healthy controls, indicating an impaired sympathovagal balance [5,7]. However, this analysis requires the use of expensive computerized systems and Holter ECG recordings. R-R interval variation (RRIV) analyses, using an electromyography device, offer an easily applicable alternative for this purpose. Although it is a simple, reliable, and nontime-consuming procedure, we came across only one study that used this technique which employed the use of RRIV's only at rest (R) and during deep breathing (D), and found reduced RRIVs at deep breathing in FM patients [19].

Due to the conflicting reports presented above, autonomic responses in FM patients need further elaboration. Also, despite extensive research, it is not known whether there is any relationship between ANS dysfunction and the severity of NP symptoms in FM patients. Therefore, we designed this study based on the above-mentioned findings and assumptions. We aimed to evaluate ANS dysfunction in drug-free FM patients using SSR and RRIV analyses and to investigate potential associations between ANS dysfunction, disease severity, and NP status in these patients. Based on previous reports, we predicted 1) increased SSR amplitudes, decreased SSR latencies, and decreased RRIVs in FM patients compared with healthy participants, 2) positive associations between SSR amplitudes and FM severity, 3) inverse associations between RRIVs and FM severity, 4) positive or inverse associations between ANS dysfunction and some somatic symptoms of FM, 5) a more pronounced increase in SSR amplitudes in a subset of FM patients with NP, leading to positive associations with NP levels, and 6) a more pronounced reduction in RRIVs in a subset of FM patients with NP. Addressing these aspects will help us to understand some of the clinical scenarios faced by FM patients and will offer new opportunities for further research regarding the treatment of this syndrome.

## MATERIALS AND METHODS

A total of 29 female patients with FM who met both the 1990 and 2010 American College of Rheumatology (ACR)

criteria and 20 age-gender matched healthy volunteers without any known systemic or neurological disease were included in the study. The patient group was selected from among the patients who applied to the Physical Therapy and Rehabilitation, Rheumatology, and Pain Medicine outpatient clinics, and the control group was selected from among the hospital staff and caregivers.

Exclusion criteria were the use of any medication that might affect the autonomic responses (antidepressants, antiepileptics, or beta or calcium channel blockers), a history of neuropsychiatric, cardiovascular, neurological, or endocrinological disorders (*i.e.*, dementia, alcohol abuse, cerebrovascular disease, diabetes mellitus, hypo- or hyperthyroidism, heart failure, syncope/orthostatic hypotension, or rhythm disorders), and presence of other diseases that may cause NP (*i.e.*, peripheral neuropathies, malignancy, chronic renal disease, or inflammatory joint disease). The local ethics committee of the Ege University approved all aspects of this study (approval number: 12-3/12). Informed consent was obtained from all patients and controls.

The severity and symptom characteristics of FM were evaluated using the ACR 2010 scales and Fibromyalgia Impact Questionnaire (FIQ) [20]. The ACR 2010 consists of 2 scales: The widespread pain index (WPI) quantifies the extent of bodily pain on a 0–19 scale by asking patients if they have had pain or tenderness in 19 different body regions. The symptom severity (SS) scale is a sum of the 0–3 scores of a series of symptoms that were characteristic of FM: fatigue, unrefreshing sleep, cognitive problems, and the extent of somatic symptom reporting, giving a total score of 0–12. The somatic symptoms considered are: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problems, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, photosensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Features of NP in FM patients were evaluated by using the Pain Detect Questionnaire (PDQ) and Douleur Neuropathique 4 questionnaire (DN-4). PDQ is a quick, simple, and reliable symptom-based screening tool to assist identification of NP [21]. It is comprised of 12 items. The first five assess the intensity and characteristics of the pain. The remaining seven questions address pain-related sensorial abnormalities: the patients were asked to rate the presence

and severity of somatosensory signs and symptoms in the following areas of pain 1) burning sensation, 2) tingling or prickling, 3) light touching, 4) sudden pain attacks, 5) thermal pain, 6) numbness, and 7) pain with slight pressure, using a six-point Likert scale. It assigns a score to the patients, which classifies pain into three groups: A score of  $\leq 12$  indicates that pain is unlikely to have a neuropathic component, a score of  $\geq 19$  indicates that pain is likely to have a neuropathic component, while a score between 13 and 18 indicates that the result is unclear. Although the PDQ has been validated in patients suffering from NP in various disorders, its criterion validity was not found to be as good in FM patients [22]. Therefore, with the aim to evaluate NP symptoms in a standard way, we analyzed the sum of the last seven questions, giving a maximum score of 35 (PDQs), not a total score.

DN-4 is a questionnaire consisting of 4 basic sections and 10 questions [23]. Seven questions are related to pain quality, and 3 questions are based on clinical evaluation. It includes both patient and clinician views. It is a widely preferred questionnaire in both clinical practice and research, because of its simplicity and accuracy. Scores above 4 points are associated with NP. It has been reported to have a specificity of 90% [24].

SSR and RRIV analyses were performed to evaluate autonomic dysfunction in both the control group and FM patients. The investigator who performed SSR and RRIV analyses was blind to the participants' clinical characteristics and NP status. Both SSR and R-R interval assessments were done using special software programs implemented to the Dantec Keypoint electromyography equipment (Dantec Medical A/S, Tonsbakken 16-18, DK-2740, Skovlunde, Denmark). The tests were carried out while the subjects were lying supine in a semi-darkened quiet room with the room temperature set to 21°C–24°C. The recordings were made in the morning, 2 hours after breakfast. The subjects were asked to avoid activities and drinks that would affect ANS function before the tests. Before starting the assessment, all subjects lay down for about 15 minutes in the electromyography (EMG) room. During the assessment, all subjects were kept awake and relaxed.

The SSRs were recorded on both hands and feet simultaneously, in response to electrical stimulation. The oscilloscope trace was set for a sweep speed of 640 msec per division, allowing an analysis time of 7.68 seconds, with filter settings at 0.5 Hz to 2 kHz. The sensitivity was adjusted between 0.5 to 2 mV per division. Disposable pregelled surface recording electrodes with a 15 × 20 mm recording area (9013S0211; Medtronic, Minneapolis, MN) were placed over the palm and sole (active) and on the dorsum of the hand or of the foot (reference), respectively.

The electrical stimuli as single square wave pulses of a 0.2 seconds duration and 10–30 mA intensity were applied to the peroneal nerve at the capitulum fibula. The stimuli were repeated with irregular inter-stimulus intervals of approximately 1 minute and break of 2–3 minutes between stimulus types to avoid a habituation of the response. Attempts were made to obtain three measurable response pairs. Amplitudes were measured from peak to peak. Latencies were measured from the onset of the stimulus artifact to the first deflection of the potential from baseline.

RRIV analyses were performed by placing two surface recording electrodes on the dorsum of both hands. After QRS complexes were detected, the peaks and the intervals between the two R waves were analyzed automatically [25]. First, RRIVs during normal breathing were recorded, while the subjects breathed synchronously for 1 minute. Then the recordings were made while the subject performed deep breathing (6 successive deep respiratory cycles of 5 seconds inspiration and 5 seconds expiration) for 1 minute. RRIV ratios during normal and deep breathing were calculated by the computer according to the following formula: The longest and shortest R-R intervals were measured. The ratio of the difference between the longest and the shortest R-R interval to the mean of all R-R intervals was multiplied by 100. Then the RRIVs were recorded while the subject performed the Valsalva maneuver for 25 seconds after 10 seconds of normal breathing, and then another 25 seconds of normal breathing. The Valsalva ratio was calculated by the computer by dividing maximum R-R interval after the Valsalva maneuver by minimum R-R interval during the Valsalva maneuver. Lastly, RRIVs in response to tilt were recorded while the subject moved to a sitting position after 10 heartbeats. The tilt ratio (30/15 ratio) was calculated as the proportion of the longest interval at the 30th heartbeat to the shortest interval at the 15th heartbeat.

## 1. Statistical analysis

The power analysis based on the preliminary data on both SSRs and RRIVs on healthy individuals showed that at least 20 subjects were required in each group in order to show a 50% difference between groups with 5% type 1 error rate and 80% power (G\*Power ver. 3.1; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) [26]. Statistical analysis was conducted by using the IBM SPSS Statistics ver. 23 (IBM Co., Armonk, NY). Descriptive and frequency analyses were performed for the demographic, clinical and electrophysiological variables. The normality of the data was tested using the Shapiro-Wilk test. Normally distributed data were presented with mean and standard deviation, non-normally distributed data were presented with median and interquartile range values. SSR amplitudes and RRIV values were not found to be normally distributed, therefore the data were analyzed using non-parametric tests. SSR latencies showed normal distribution, thus parametric tests were used for analyses. Since the SSR amplitudes and latencies did not differ statistically significantly between the two sides, the average of the potentials obtained in both hands (SSR-hands) and feet (SSR-feet) was considered. The intergroup comparisons were analyzed using the Mann-Whitney *U*-test and the relationships of data with clinical variables were tested using Spearman correlation analysis. Statistical significance was defined as  $P < 0.05$ .

## RESULTS

All FM patients and controls were female, with a mean age of  $37.5 \pm 7.6$  years and  $38.2 \pm 13.8$  years, respectively. There were no significant differences between the groups regarding age ( $P = 0.585$ ).

Comparison of SSR and RRIV data between FM patients and controls are seen in **Table 1**. SSR amplitudes were found to be significantly higher while SSR latencies were

**Table 1.** SSR and RRIV data in FM patients and controls

| Variable                        | FM patients (n = 29) | Controls (n = 20)   | P value |
|---------------------------------|----------------------|---------------------|---------|
| SSR amplitude (hand) ( $\mu$ V) | 3,620 (2,455–6,151)  | 2,400 (1,914–4,175) | < 0.001 |
| SSR latency (hand) (ms)         | 1,429 $\pm$ 183      | 1,528 $\pm$ 144     | 0.040   |
| SSR amplitude (foot) ( $\mu$ V) | 2,165 (1,505–3,092)  | 941 (786–118)       | < 0.001 |
| SSR latency (foot) (ms)         | 1,893 $\pm$ 255      | 1,984 $\pm$ 464     | 0.007   |
| RRIV normal breathing           | 13 (8–21.7)          | 15.5 (12.2–25)      | 0.154   |
| RRIV deep breathing             | 28 (21.5–35.7)       | 36.5 (31.2–38)      | 0.063   |
| RRIV Valsalva                   | 1.29 (1.20–1.57)     | 1.72 (1.50–2.53)    | < 0.001 |
| RRIV tilt                       | 1.08 (1.03–1.12)     | 1.53 (1.22–2.72)    | < 0.001 |

Values are presented as median (interquartile range) or mean  $\pm$  standard deviation.

SSR: sympathetic skin response, RRIV: R-R interval variation, FM: fibromyalgia.



**Table 2.** Relations between disease severity, somatic symptoms, and SSRs in patients with FM

| Variable             | SSR-hand amplitude |         | SSR-feet amplitude |         | SSR-hand latency |         | SSR-feet latency |         |
|----------------------|--------------------|---------|--------------------|---------|------------------|---------|------------------|---------|
|                      | Rho                | P value | Rho                | P value | Rho              | P value | Rho              | P value |
| ACR 2010             |                    |         |                    |         |                  |         |                  |         |
| WPI                  | 0.560              | 0.002   | 0.397              | 0.044   | 0.011            | 0.954   | 0.242            | 0.215   |
| SSS                  | 0.391              | 0.044   | 0.434              | 0.021   | 0.158            | 0.421   | 0.283            | 0.145   |
| Total score          | 0.521              | 0.004   | 0.489              | 0.008   | 0.039            | 0.843   | 0.231            | 0.238   |
| Somatic symptoms     |                    |         |                    |         |                  |         |                  |         |
| Fatigue              | 0.511              | 0.005   | 0.218              | 0.265   | 0.224            | 0.291   | 0.241            | 0.128   |
| Unrefreshed sleep    | 0.455              | 0.044   | 0.055              | 0.783   | 0.062            | 0.755   | 0.100            | 0.813   |
| Dizziness            | 0.424              | 0.024   | 0.226              | 0.247   | -0.014           | 0.944   | 0.120            | 0.542   |
| Painful urination    | 0.412              | 0.029   | 0.393              | 0.039   | -0.299           | 0.122   | -0.219           | 0.263   |
| Insomnia             | 0.101              | 0.610   | 0.394              | 0.038   | -0.002           | 0.991   | 0.144            | 0.464   |
| Raynaud's phenomenon | 0.239              | 0.220   | 0.328              | 0.042   | -0.583           | 0.001   | -0.104           | 0.598   |
| Sun sensitivity      | 0.098              | 0.620   | 0.368              | 0.046   | -0.104           | 0.600   | 0.121            | 0.540   |
| FIQ score            | 0.427              | 0.042   | 0.323              | 0.036   | 0.065            | 0.587   | 0.195            | 0.357   |

ACR: American College of Rheumatology, WPI: widespread pain index, SSS: symptom severity scale, FIQ: Fibromyalgia Impact Questionnaire, SSR: sympathetic skin response, FM: fibromyalgia.

**Table 3.** Relations between disease severity and RRIVs in patients with FM

| Variable    | RRIV normal breathing |         | RRIV deep breathing |         | RRIV Valsalva |         | RRIV tilt |         |
|-------------|-----------------------|---------|---------------------|---------|---------------|---------|-----------|---------|
|             | Rho                   | P value | Rho                 | P value | Rho           | P value | Rho       | P value |
| ACR 2010    |                       |         |                     |         |               |         |           |         |
| WPI         | 0.172                 | 0.380   | 0.101               | 0.611   | 0.000         | 0.999   | -0.245    | 0.208   |
| SSS         | -0.097                | 0.624   | 0.116               | 0.558   | -0.067        | 0.736   | 0.092     | 0.641   |
| Total score | 0.097                 | 0.824   | -0.011              | 0.956   | 0.016         | 0.936   | 0.016     | 0.270   |
| FIQ score   | 0.062                 | 0.755   | -0.066              | 0.739   | -0.139        | 0.481   | 0.067     | 0.736   |

ACR: American College of Rheumatology, WPI: widespread pain index, SSS: symptom severity scale, FIQ: Fibromyalgia Impact Questionnaire, RRIV: R-R interval variation, FM: fibromyalgia.

found to be significantly shorter in FM patients than those in controls (Table 1). RRIV ratios during normal and deep breathing tended to be lower in FM patients comparing to the controls, but the difference was not statistically significant. On the other hand, RRIVs during the Valsalva and Tilt tests were found to be significantly lower in FM patients than those in controls. SSR amplitudes showed significantly positive correlations with the ACR 2010 scales and FIQ (Table 2), while SSR latencies and RRIVs did not show any significant correlations with these parameters (Tables 2, 3).

The most frequently reported somatic symptoms by patients were fatigue (100%; 42% very severe), unrefreshed sleep (93%; 25% very severe), and trouble thinking or remembering (90%), while difficulty in hearing (10%) and loss of appetite (13%) were the most rarely reported. Correlation analyses between the somatic symptoms, SSR, and RRIV data showed that SSR-hand amplitudes were significantly positively correlated with fatigue, unrefreshed sleep, dizziness, and painful urination (Tables 2, 3); SSR-feet amplitudes were significantly positively correlated with insomnia, painful urination, Raynaud's phenomenon, and photosensitivity (Table 2); SSR-hand

**Table 4.** Relations between neuropathic pain, SSRs and RRIVs in patients with FM

| Variable              | PDQ    |         | DN-4   |         |
|-----------------------|--------|---------|--------|---------|
|                       | Rho    | P value | Rho    | P value |
| SSR amplitude (hand)  | -0.366 | 0.056   | -0.194 | 0.408   |
| SSR amplitude (feet)  | 0.236  | 0.228   | -0.198 | 0.544   |
| SSR latency (hand)    | 0.134  | 0.498   | 0.092  | 0.782   |
| SSR latency (feet)    | 0.176  | 0.371   | 0.102  | 0.675   |
| RRIV normal breathing | -0.102 | 0.605   | -0.095 | 0.780   |
| RRIV deep breathing   | -0.067 | 0.735   | -0.055 | 0.780   |
| RRIV Valsalva         | -0.150 | 0.445   | -0.150 | 0.446   |
| RRIV tilt             | -0.064 | 0.765   | -0.026 | 0.896   |

PDQ: Pain Detect Questionnaire, DN-4: Douleur Neuropathique 4 questionnaire, SSR: sympathetic skin response, RRIV: R-R interval variation, FM: fibromyalgia.

latencies were significantly inversely correlated only with Raynaud's phenomenon (Table 2); while RRIV data were not significantly correlated with any symptoms.

The mean PDQ score was  $15.3 \pm 6.5$  (0 to 27), and the mean DN-4 score was  $4.4 \pm 2$  (0 to 9) in patients with FM. Although the SSR hand and feet amplitudes and RRIV variables tended to show negative correlations with the

PDQ and DN-4 scores, these relations did not reach statistical significance (Table 4). SSR amplitudes showed no significant associations with any of the neuropathic symptoms in question. SSR latencies did not show statistically significant correlations with PDQ and DN-4 scores, and with the symptoms.

## DISCUSSION

The results of this study showed that patients with FM have ANS dysfunction with an increase in sympathetic activity and a decrease in parasympathetic activity compared to healthy controls. Sympathetic activity, as measured with SSR amplitudes was found to be associated with the severity of FM. On the other hand, although not statistically significant, NP severity tended to be associated with a decrease in sympathetic and parasympathetic activities in FM patients.

In this study, SSR amplitudes were found to be significantly higher while SSR latencies were significantly shorter in FM patients compared to controls. Given that SSR is controlled exclusively by sympathetic cholinergic terminals, these findings suggest increased sympathetic activity in FM patients. This result is in accordance with reports of increased SSR amplitudes in FM although other studies found lower amplitudes indicating decreased sympathetic activity [16,17,27]. These conflicting results between different studies may be explained by the well-known intra-individual variations for SSR testing, the significant heterogeneity in psychophysiological profiles among FM patients, and the influence of other confounders such as comorbidities and medications used [28].

On the other hand, we found that FM patients had depressed RRIVs in response to all stimuli compared to controls, reaching statistical significance in response to the Valsalva and tilt maneuvers. Since each of RRIV tests has its own advantages and disadvantages, the results should be interpreted after understanding the characteristics of each test. RRIVs at rest and during deep breathing are the result of the balance between sympathetic and parasympathetic neural effects on sino-atrial node automatism, so the expiration/inspiration ratio is assumed to be a sensitive index of cardiac efferent parasympathetic function [18]. While HRV analysis is less sensitive in detecting the potential ANS dysfunction, it is a test that is performed in a more stable condition. The Valsalva ratio is based on reflex changes in RRIVs during and after the Valsalva maneuver, which elicits a complex series of hemodynamic events. It can also be used as an effective measure of parasympathetic integrity [29]. RRIV in response to tilt reflects different mechanisms of neural reflexes. It is a complex reflex

response of the cardiovascular system, involving not only the vagus nerve, but also hemodynamic modifications, so it is also affected by sympathetic stimulation. Therefore, a ratio of 30:15 has been proposed to standardize an autonomic test of parasympathetic division [29]. While not reaching significance in this study, reductions of RRIVs at rest and during deep breathing in FM patients may support the previous studies using Holter recordings and EMG [5-7,30]. To the best of the authors' knowledge, the present study is the first to measure RRIVs in response to the Valsalva and tilt maneuvers by using EMG in FM patients. Indeed, RRIV reductions in response to the Valsalva and tilt maneuvers were much more pronounced and significant in FM patients compared to controls. This finding suggests that FM patients are slow to adapt to standing and to environmental changes. Thus, with these findings, the authors further reinforced and supported the previous reports showing aberrant adaptation of autonomic cardiovascular responses to orthostatic changes in FM patients [7].

An important finding of this study was that sympathetic activity as measured by SSR amplitudes showed significant positive associations with widespread pain, severity of symptoms, and overall FMS severity. However, similar relationships were not observed for SSR latencies. This may be due to the fact that height, which we did not control as a confounding factor, may influence the onset latency of SSR but not the amplitudes [30]. This may also be due to the notion that the latency measurements of the SSR have little value in diseases in which the overactivity of the sympathetic system is the main mechanism, as the efferent unmyelinated fibers account for most of the latency [31,32].

To the authors' knowledge, the relationship between widespread pain and ANS dysfunction has not been demonstrated before. There are studies demonstrating that sympathetic activity was linearly correlated with chronic pain intensity, number of tender points, and FIQ [8,17]. Although we did not demonstrate a significant relationship with widespread pain and parasympathetic activity, there are some studies showing an inverse relationship between lower cardiac baroreflex functioning and higher levels of clinical pain [11]. We also found significant correlations with non-pain related symptoms of FM including fatigue, unrefreshing sleep, dizziness, painful urination, insomnia, sun sensitivity, and Raynaud's phenomenon. Such relationships have been demonstrated in many studies [3,7,33,34]. These studies and the present study may support the hypothesis that increased sympathetic activity may contribute to pain and other clinical problems associated with FM [34]. According to this hypothesis, sympathetic overactivity in FM might be due to a sympathetic drive of the primary central nervous system [7] and can

take part in the central sensitization process by sensitizing nociceptors to catecholamines, resulting in increased nociceptive firing and hyperexcitability of the dorsal root ganglia [35].

Some authors have also suggested that the fatigue and widespread pain might be secondary to peripheral tissue ischemia produced by excessive vascular tone, due to sympathetically mediated vasoconstriction [36]. In addition, the stress response also plays an important role in pain and ANS dysfunction, as FM patients report highly stressful life events and increased sympathetic responses to stress [4,28]. It has been suggested that, due to a ceiling effect, the hyperactive sympathetic nervous system of such patients becomes unable to further respond to different stressors, which may explain pain and other clinical problems they suffer from [34]. Although these studies and the present study support the role of ANS dysfunction in the pathogenesis of FM, the causality of such an association cannot be judged by these findings, because chronic stressor "pain" may also lead to increased sympathetic activity [37]. Therefore, further research is needed to establish this causality considering confounding factors. If this causation can be demonstrated, it could have important clinical implications, as the reduction of excessive sympathetic activity may result in clinical improvement. This may potentially facilitate the development of future interventions and pharmacotherapy targeting ANS dysfunction in FM.

To the authors' knowledge, this is the first study which addressed associations between ANS dysfunction and magnitude of NP in FM patients. Contrary to the authors' hypothesis, we found a decreasing trend in SSR amplitudes and RRIVs and an increasing trend in SSR latencies with NP severity. While the statistical insignificance can shadow the strength of these findings, this may seem to contradict the previous hypothesis that FM is a sympathetically maintained NP syndrome [35,38]. These findings may also partially explain the conflicting results in the literature regarding the ANS dysfunction pattern in FM patients.

It may be possible to interpret this finding in the context of impaired small fiber function in patients with FM and the dysautonomia-neuropathic hypothesis [12–14,39]. This may also support the notion that there may be a distinct phenotype involving small fiber neuropathy (SFN) in FM. There is increasing evidence for involvement of the peripheral nervous system with a high prevalence of small fiber pathology in FM. A recent meta-analysis reported that the pooled prevalence of SFN in FM was 49% with moderate heterogeneity [40]. The presence of SFN has been shown to be congruent with the increased rate of NP symptoms [40]. However, diagnosing SFN remains a challenge as regular

nerve conduction studies only evaluate large myelinated nerve fibers, and the pathophysiology of SFN is complex, and small fibers have a wide range of functions. Although methods such as laser-evoked potentials, quantitative sensory testing, or corneal biopsy have been used to diagnose SFN, each focuses on specific areas, and they are not well-correlated with each other [41]. Still, a recent study showed that the NP questionnaires have a good concordance with SFN in patients with FMS, which may help the investigators confirm its presence more easily as the literature grows [42].

SSR and RRIV tests have also been suggested to be useful and sensitive electrophysiologic tests for the early diagnosis of diabetic small fiber neuropathy [43]. When the ANS is affected by SFN, the SSR latency will be delayed, and the SSR amplitude will decrease. RRIVs have also been found to be significantly associated with validated measures of large and small fiber neuropathy [44]. However, there are caveats that SFN cannot be confirmed based on abnormal SSR and RRIVs alone, due to their low sensitivity in diagnosing SFN. Although this study does not provide convincing evidence for the presence of SFN, it will encourage further studies evaluating the associations between ANS dysfunction and the presence of SFN, confirmed by more valid and reliable tests.

There are some strengths and limitations of this study. The main strength is that it is the first study to address the relationships between ANS dysfunction and the severity of NP, and to measure RRIVs in response to Valsalva and tilt maneuvers using EMG in FM patients. The use of a female-only sample and age-matched control group and inclusion of the patients who were drug-free and had no comorbidities are the other strengths that eliminate possible confounders on autonomic testing [45]. The most prominent limitation of this study is the small sample size, due to rigid inclusion and exclusion criteria. Since a smaller fraction of FM patients were eligible, this may have a hindering effect on the results. Also, the criteria excluded male patients and those with comorbidities, limiting the generalizability of the results.

The results of this study showed that patients with FM have ANS dysfunction with an increase in sympathetic activity and a decrease in parasympathetic activity compared to healthy controls. Sympathetic activity, as measured with SSR amplitudes was found to be associated with the severity of FM. On the other hand, although not statistically significant, NP severity tended to be associated with a decrease in sympathetic and parasympathetic activities in FM patients.

In conclusion, ANS dysfunction may play a role in the pathophysiology of FM. However, based on available studies including the present one, it cannot be determined

whether chronic pain is a cause or a consequence of ANS dysfunction. Therefore, further research is needed to establish this causality considering confounding factors. Although lacking statistical significance, the decreased sympathetic and parasympathetic responses in the patients exhibiting NP characteristics may be a sign of small fiber involvement in these patients. This finding is contrary to the authors' hypothesis and contradicts previous reports suggesting that FM is a sympathetically maintained NP. Instead, it may support the concept of impaired small fiber function in FM patients with NP features. These findings may also partially explain the conflicting results in the literature regarding the ANS dysfunction pattern in FM patients. Future studies should focus on neural involvement with higher numbers of participants to elucidate the possible involvements of these mechanisms. These studies may potentially facilitate the development of future interventions and pharmacotherapy in treatment of FM.

## DATA AVAILABILITY

The datasets supporting the finding of this study are available from the corresponding author upon reasonable request.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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