ORIGINAL ARTICLE

R-R Interval Variation and Sympathetic Skin Response in Fibromyalgia

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Background. This study proposed to assess the autonomic nervous system (ANS) functions in fibromyalgia (FM) by using two electrophysiological tests, sympathetic skin response (SSR) and the heart rate variability named R-R interval variation (RRIV).

Methods. Sympathetic skin response and RRIV were studied in 29 female patients with FM and 22 healthy age-matched female controls. R-R interval variation at rest (R%), during deep breathing (D%), the difference between D% and R% (D–R) and the ratio of D–R% (D/R) were determined. Pain threshold was measured using a mechanical algometer.

Results. R-R interval variation at rest (R%) and D/R did not show significant difference between patients and controls, whereas D% and D–R were significantly lower in patients compared to controls. SSR latencies of patients' hands and feet had no significant difference compared to controls' hand and feet SSR latencies. SSR latencies of patients' hands correlated significantly with control point score, total myalgic score, Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating Scale. Sympathetic skin response latencies of patients' feet correlated only with HARS.

Conclusions. Analysis of heart rate variability may be useful and complementary to clinical examination in patients with symptoms of dysfunction in cardiovascular reflex pathways. © 2006 IMSS. Published by Elsevier Inc.

Key Words: Sympathetic skin response, Heart rate variability, Autonomic dysfunction, Fibromyalgia.

Fibromyalgia (FM) is a common, chronic, widespread pain syndrome usually associated with other somatic and psychological symptoms including fatigue, poor sleep, cognitive difficulties, psychologic distress and features of irritable bowel, Raynaud's phenomenon or bladder dysfunction (1). The diversity of symptoms and poorly understood etiology make FM a frustrating condition.

Autonomic nervous system (ANS) is the portion of the nervous system that controls the functions of the body organs and systems, i.e., regulate body temperature, heart beat rate, bowel and bladder tone, etc. Its control is autonomic, in other words it works below the level of consciousness and is activated by centers located in the central nervous system. The ANS is an important component of human stress response and works closely with hypothalamic–pituitary–adrenal (HPA) axis (2–5).

Recent reports have shown that aberrant ANS function may be responsible for some of the symptoms seen in FM (2,3,5). While assessing ANS in FM, investigators have used various techniques, some of which have assessed isolated components of ANS whereas others have portrayed how individuals respond to "stressors" that involve the ANS (2,3,5).

The aim of this study was to assess ANS functions in FM by using two electrophysiological tests of autonomic function, sympathetic skin response (SSR), and the heart rate variability named R-R interval variation (RRIV).

Materials and Methods

Twenty nine female patients who met the 1990 American College of Rheumatology (ACR) criteria for the classification of FM (1) and 22 healthy female controls matched for age, height and weight were enrolled. The patients and controls volunteered to participate in the study and gave their informed consent. None of the patients was under

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anti-depressant treatment, muscle relaxants or analgesics and were included only if they had stopped using them at least 3 weeks before the study. The inclusion criteria for the study group comprised a negative history for heavy cigarette smoking, neuropsychiatric disorders (dementia, cerebrovascular disease, alcohol abuse, severe depression), psychoactive or cardiovascular drug (beta or calcium channel blockers) treatment, and other neurological or endocrinological (i.e., diabetes mellitus, hypo- or hyperthyroidism) disorders. An informative handout advising stopping caffeine and alcohol intake and having restorative sleep 1 day before the study was given to the patients and controls. To rule out peripheral neuropathy, motor, sensory and F-wave response studies were carried out using standardized electrophysiological techniques in all patients and controls. In upper extremities medial and ulnar nerve sensorial and motor conduction velocity were examined. In lower extremities tibial and peroneal motor conduction velocity and sural nerve sensorial conduction velocity were examined.

Assessing Myalgic Scores

The pressure pain threshold (PPT) measurements of patients were performed in the same room in the early afternoon by using a mechanical algometer. The same doctor carried out PPT measurements. Before the evaluations, patients were informed of the procedure. Pain threshold was explained as the amount of pressure adequate to induce a sensation of discomfort, and it was explained to patients that the aim was to determine pain threshold but not pain tolerance.

Eighteen tender points (TPs) and three control points (CPs) were evaluated using the methods, which were previously defined and used elsewhere (6–8). A positive TP was defined as a point at which the subject had mild or great pain with <4 kg/cm^2 pressure. The sum of the PPTs of 21 points (18 TPs, 3 CPs) was calculated as the total myalgic score (TMS in kg).

The Hamilton Depression Rating Scale (HDRS) (9) and Hamilton Anxiety Rating Scale (HARS) (10) were used to evaluate the affective condition of patients with FM. Patients were administered the Turkish version of the Fibromyalgia Impact Questionnaire (FIQ) (11). All measurements were performed on the same day as electrophysiological tests. Patients were also screened for distinctive features of FM like fatigue, sleep disorders/non-restorative sleep, paresthesia, headache, Raynaud's phenomena, bladder dysfunction (presence of voiding difficulties, frequency of voiding, etc.), sicca symptoms, irritable bowel syndrome, orthostatic intolerance (lightheadedness, concentration difficulties, syncope or near syncope on standing).

R-R Interval Variation

All patients were studied in the supine position using equipment from Dantec, Keypoint (Medtronic, Denmark) by the same neurologist who was blinded to the patients' and controls' identity and clinical data. Recordings were made using two surface electrodes placed on the chest or alternatively to the dorsum of each hand. A metal strap electrode around one wrist was used as the ground electrode. Using the triggering mode and delay line, the oscilloscope display was adjusted by adjusting the trigger sensitivity and sweep speed so that two QRS complexes were displayed on the screen. As the first displayed complex is the triggering potential, the variation in timing of the second complex represents the variation in the R-R interval. Five groups of 20 sweeps were recorded at rest and two during forced deep breathing at six breaths per minute. The bandpass was 5–1000 Hz, the sensitivity 0.5 mV and the sweep duration was 0.2–1 sec. The recordings and calculations were performed by the computer software. The following algorithm was used to analyze R-R variation (RRmax–RRmin) $\times$ 100/RRmean (the difference between the shortest and the longest RR intervals during 1 min given in percent of the mean of all maximal and minimal peaks). Details of this method have been published elsewhere (12,13).

The average of five recordings at rest was termed as R% and that of two recordings during deep breathing as D%. The difference between D% and R% (D–R) and the ratio of D–R% (D/R) were also calculated.

RRIV responses at rest and deep breathing were considered abnormal when beyond two standard deviations lower than mean responses of age-matched normal controls (14,15).

Sympathetic Skin Response

The SSR was studied using the standard method (16). The skin temperature was maintained at 32°C (room temperature stabilized at 25–26°C). A standard electromyographic active electrode was attached to the palm and sole and the reference electrode to the dorsum of the hand and foot. The same EMG equipment was used (Dantec, Keypoint, Medtronic). The stimuli used were single electrical stimulus at the wrist contralateral to the recording side. Stimuli were delivered unexpectedly and in irregular intervals of more than 1 min to prevent habituation. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection and expressed in seconds. The amplitude was measured from the baseline to the negative peak and expressed in mV. The response was considered absent if no consistent voltage change occurred using a sensitivity of 50 µV per division after three trials at maximum stimuli intensity. In our study, the amplitudes were not included in the analysis because the amplitudes had extent variability even in the same subject in repeated measurements due to possible habituation phenomena. Response latencies were considered pathological when more than 2 SD above the mean latency of the control group.

Statistics

Results are expressed as mean ± SD, and differences between the two groups were assessed using t test. Pearson correlation coefficients were used to assess relationship between parameters. Two-tailed p value of <0.05 was considered statistically significant. Statistics Package for Social Sciences (SPSS Inc., Chicago, IL) was used for the analyses.

Results

RRIV and SSR were successfully obtained in all patients and healthy controls. Patients had a disease duration of 5.0 ± 3.3 years, and mean age was 39.6 ± 8.6 in patients and 34.6 ± 9.4 in controls. There was no significant difference in age, height and weight between patients and controls. Patients' clinical variables and relationship with sympathetic skin response latencies of hands and feet are shown in Table 1. Mean values of RRIV for patients and controls are shown in Table 2. R-R interval variation at rest and the ratio of D–R% did not show significant differences between patients and controls whereas RRIV at deep breath and the difference between D% and R% were significantly lower in patients compared to controls (Table 2).

SSR latencies of hands and feet were obtained in patients and controls. Mean latencies of SSR of hand and foot for the patients and controls are shown in Table 3, and there was no significant difference between patients and controls.

R-R interval variation at rest and deep breathing negatively correlated with age in control group but not in patient group ($r = -0.49$, $p = 0.02$ and $r = -0.43$, $p = 0.05$, respectively). Patients SSR latencies for hands correlated significantly with CPS ($r = 0.56$, $p = 0.002$), TMS ($r = 0.46$, $p = 0.012$), HARS ($r = 0.50$, $p = 0.006$) and HDRS ($r = 0.52$, $p = 0.004$). Sympathetic skin response latencies of patients' feet correlated only with HARS ($r = 0.42$, $p = 0.024$).

R-R interval variation values during deep-breathing were abnormal in seven patients (24%), of whom six had orthostatic intolerance and sleep disorders, six had sicca symptoms, three had irritable bowel syndrome, four had bladder dysfunction, and one had Raynaud's phenomena.

Discussion

Despite a growing body of research, FM continues to be a chronic pain syndrome without a clear etiology. Recent studies have provided convincing evidence for central pain processing abnormalities that share some features of neuropathic pain syndromes in FM. Some of these abnormalities are hyperalgesia, allodynia, abnormal activation of pain-related brain regions, wind-up (temporal summation of second pain) and neuroendocrine abnormalities (17). On the other hand, some authors suggested that autonomic nervous system dysfunction may play a role in the pathogenesis of FM based on clinical and experimental research documenting autonomic nervous system involvement in FM patients (2,3,5). Autonomic dysfunction has been suggested to be associated with some of the FM symptoms as fatigue, morning stiffness, sleep disorders, anxiety, cold and clammy hands, sicca symptoms and intestinal irritability (2,4,5,18). The ANS, particularly sympathetic nervous system, is also an important component of human stress response and acts closely with the HPA axis (3).

ANS involvement in FM was first described by Bengtsson and Bengtsson who reported improvement in pain and number of tender points in response to stellate ganglion blockade in a controlled trial (19). Based on their findings, the researchers suggested that aberrant muscle sympathetic nerve activity might be a possible mechanism in FM pathogenesis (19). Although Elam et al. reported similar resting sympathetic nerve activity between patients and controls in response to brief isometric muscle contraction, muscle ischemia and mental stress (20), Wachter showed muscle dampening in pendulum test possibly due to sympathetic stimulation of intrafusal muscle fibers (21). Martinez-Lavin suggested that sympathetic nervous system dysfunction may explain complex symptomatology of FM, i.e., sympathetic hyperactivity may explain endocrine abnormalities like HPA axis dysfunction, sleep disorders, sicca symptoms, and pseudo-Raynaud's phenomena (5,18). In our patients, we found similar SSR latencies compared to matched controls. On the other hand, close correlation between SSR latencies in hands and clinical measurements renders an interesting clinical scenario that the sympathetic nervous system may play an important role in FM

Table 1. Clinical variables of patients and relationship with sympathetic skin response latencies

	Mean (SD)	Min-max	Palm latency r (p)	Sole latency r (p)
CPS	12.9 (2.1)	8.8–17.5	0.56 (0.002)	0.20 (NS)
TMS	79.4 (10.4)	57.7–101.4	0.46 (0.012)	−0.10 (NS)
HDRS	18.2 (5.7)	6–28	0.52 (0.004)	0.33 (NS)
HARS	20.9 (8.7)	8–38	0.50 (0.006)	0.42 (0.024)
FIQ-first item	0.9 (0.4)	0–1.75	−0.07 (NS)	−0.05 (NS)
FIQ-fifth item	6.8 (1.4)	4.3–9.5	−0.15 (NS)	−0.06 (NS)

CPS, control point score; TMS, total myalgic score; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; FIQ-first item, Fibromyalgia Impact Questionnaire first item score (patient's physical functioning), FIQ-fifth item, Fibromyalgia Impact Questionnaire first item (visual analog scale of pain); NS, not significant; r, correlation coefficient.

Table 2. Mean R-R interval variation values in patients and controls

	Mean (SD) (patients)	Mean (SD) (controls)	*p*
R%	15.7 (6.2)	18.6 (5.9)	NS
D%	21.8 (8.1)	31.4 (7.7)	0.0001
D–R	6.1 (7.0)	12.7 (7.7)	0.004
D/R	1.5 (0.6)	1.8 (0.8)	NS

R%, R-R interval variation at rest; D%, during deep breathing; D–R, the difference between D% and R%; D/R, the ratio of D–R%.

symptomatology. The fact that intra-individual variation of amplitudes is considerably high, we reasonably preferred to use latencies. The intra-individual variation for latency has been reported in a range of 2–22% and for amplitudes 2–48% in different studies (21–24).

Regarding microcirculation abnormalities, which are in close relation with autonomic nervous system, contradictory results have been reported in different studies. Some of these studies suggested diminished vasoconstrictor response to cold and/or noise stimuli (25,26), whereas others reported contradictory findings in vasoconstrictor response (27,28).

R-R interval variation is based on the variability of heart rate in a relaxed state and following hyperventilation (2,29). Indeed, heart rate variability is the result of the instantaneous relationship between excitatory, i.e., sympathetic, and inhibitory, i.e., parasympathetic, neural influences on the sino-atrial node automatism.

Martinez-Lavin et al. studied tilt table test in 19 female patients with FM and 19 age-matched controls. These researchers found that FM patients failed to increase their low frequency band power after adopting the upright posture and they interpreted this result as an orthostatic sympathetic derangement (30). These results were confirmed by other researchers using different types of maneuvers (31–34). A further study by Martinez-Lavin and colleagues demonstrated that FM patients had less heart rate variability and altered circadian variation of sympathetic/parasympathetic balance (35).

The major limitation of this study and also the method is that R-R interval variation is computer drawn from a very short period of recording of heart beat (nearly 1 min). A longer period (i.e., 200–500 beats) would be more valuable and help draw more firm conclusions.

Our study revealed lower values of heart rate variability during deep breathing and difference between D% and R%. Seven patients (24%) had abnormal RRIV, most of whom had orthostatic intolerance, sleep disorders and sicca symptoms.

Table 3. Sympathetic skin response latencies in patients and controls

	Mean (SD) (patients)	Mean (SD) (controls)	*p*
Palm latency (sec)	1.20 (0.3)	1.21 (0.3)	NS
Sole latency (sec)	1.77 (0.5)	1.86 (0.6)	NS

SD, standard deviation; NS, not significant.

Together these findings may be interpreted that autonomic nervous system dysfunction exists in FM and may be responsible for some of the symptoms of this disorder. Additionally, this study included patients who were not under medication, in other words, drug-free patients who made the results of this study more valuable.

In summary, these two practical methods, RRIV and SSR, may help clinicians to evaluate involvement in specific subsystems of ANS like dysfunction of cardiovascular reflex pathways and sudomotor system. Analysis of heart rate variability may be useful and complementary to clinical evaluation in patients with symptoms of dysfunction in cardiovascular reflex pathways.

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