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RESEARCH ARTICLE

A comprehensive study of autonomic dysfunction in the fibromyalgia patients

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Abstract
Objectives The hypothesis of autonomic nervous system involvement in pathophysiology in the patients with fibromyalgia has been addressed and tested time and again but the existing reports are both contradictory and inconclusive. A complete knowledge of the degree of autonomic dysfunction in fibromyalgia patients would be more substantial. We conducted a comprehensive non-invasive study to investigate the complete autonomic profile of female patients with fibromyalgia.
Method An autonomic function test using a standard battery and heart rate variability analysis in the 42 fibromyalgia patients as well as 42 age matched healthy controls was performed. Both autonomic activity (tone) and reactivity were measured. Autonomic tone (both time and frequency domain parameters) was measured using heart rate variability (HRV) analysis. Autonomic reactivity was measured using a standard battery of autonomic function tests.
Results Resting blood pressure (both systolic and diastolic) was significantly higher in the fibromyalgia patients than controls. The time domain variables and HF% as recorded by HRV were significantly lower in the patients than the controls. The autonomic reactivity for sympathetic and parasympathetic nervous system was found to be within normal limits.
Interpretation The cardiac autonomic function is normal and the autonomic reflex arc seems to be intact in the patients with fibromyalgia.

Keywords Fibromyalgia · Autonomic nervous system · Pain · Heart rate variability

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Introduction

Fibromyalgia is a debilitating psychosomatic illness with widespread pain as its hallmark. Autonomic abnormality has been documented in conditions closely allied to fibromyalgia syndrome such as irritable bowel syndrome, chronic fatigue syndrome and migraine headache [1]. There are sporadic reports of the autonomic nervous system dysfunction in the etiopathogenesis of fibromyalgia. The stellate (sympathetic) ganglia blockade with bupivacaine alleviates rest pain and decreases the number of tender points among the fibromyalgia patients [2]. Similarly, a significantly higher intensity of norepinephrine-evoked pain in fibromyalgia patients when compared to rheumatoid arthritis patients and healthy controls has been reported [3] suggesting that sympathetic nervous system is involved in pathophysiology of fibromyalgia. The heart rate variability (HRV) analysis results corroborate these findings further and show that fibromyalgia patients have a baseline sympathetic hyperactivity. A 24 h HRV analysis in a circadian-variation study has shown an increased nocturnal predominance of the low-frequency band oscillations indicating an exaggerated sympathetic modulation of the sinus node [4]. Impaired sympathetic reactivity to orthostatic stress is also seen in fibromyalgia patients [5]. Patients with fibromyalgia are hypo reactive to various other sympathetic stimuli such as auditory stimulation test

(80 dB, 1,000 Hz, 2 s sounds), cold pressor test at 10 and 4°C [6, 7] and gravitational stress using a tilt table [8]. However, study of cardiovascular reactivity utilizing a head-up tilt test does not reveal a specific fibromyalgia-associated abnormality as compared to controls [9]. Patients with fibromyalgia have a higher than expected rate of a positive Nielson test (cold-induced increase in finger systolic blood pressure), along with an increase in the number of α_2 adrenergic receptors on thrombocytes [10]. A cold provocation test induces a significant degree of vasospasm in fibromyalgia patients as observed by capillary videomicroscopy of the nail folds [11].

A generalized deconditioning due to inactivity because of pain and fatigue/muscle damage or both has been recognized as important cause for symptoms in fibromyalgia patients. Deconditioning of the muscles leading to an altered state of autonomic regulation in the fibromyalgia patients remains a focus of debate. Fibromyalgia appears to be a situation of autonomic dysfunction where both limbs of autonomic nervous system (sympathetic and parasympathetic) are differentially involved. Autonomic dysfunction also explains the diverse clinical manifestations of fibromyalgia like sleep disorders, anxiety, Raynaud's-like phenomenon, Sicca symptoms and intestinal irritability. We carried out a detailed analysis of the autonomic function in fibromyalgia patients using a standard battery of autonomic function tests and heart rate variability analysis. A standard battery of non-invasive tests appears to be a logical approach because it assures comparison of related cardiovascular parameters of both limbs (i.e. sympathetic and parasympathetic) of the autonomic nervous system.

Methods

Subjects

The study was conducted at the Autonomic Function Laboratory, Department of Physiology, AIIMS, New Delhi. The study protocol was approved by the ethics committee of the Institute. Informed consent was obtained from all the participants (both patients and healthy controls) prior to the study.

Subjects' selection

Patients

In the present study 42 well diagnosed female patients of primary fibromyalgia conforming to the American College of Rheumatology (ACR) diagnostic criteria [12] were recruited. They were referred to the autonomic function lab, Department of Physiology, AIIMS by the Rheumatology expert, Rheumatology Clinic, Department of Medicine, AIIMS, New Delhi after the use of rigorous diagnostic criteria. Only female patients were recruited in the study primarily for two reasons: (1) to avoid the probable effects of autonomic differences between genders and (2) the female preponderance in fibromyalgia (prevalence is 3.4% among women and 0.5% in men) [13]. The patients were subjected to extensive biochemical investigations and serum electrolyte measurements. The results of complete blood count, Westergren erythrocytic sedimentation rate, muscle enzymes, rheumatoid factor, thyroid function tests and serum electrolytes were normal in the patients. Patients with a history of hypertension, diabetes mellitus, coronary artery disease, hypovolemia, adrenal insufficiency, cardiomyopathies, congenital cardiac disease, malignancy and autoimmune diseases were excluded from the study. Furthermore, patients with a history of smoking, alcoholism and drug intake (anticholinergics and antidepressants for at least 4 weeks prior to the study) were also not included. Exclusion criteria also included those women who were pregnant or taking oral contraceptive pills or hormonal replacement therapy. All the patients were requested to refrain from analgesics on the day of the examination.

Healthy controls

The control group comprised of 42 healthy females who had no significant past medical history. The controls were selected on the basis of the same exclusion criteria as stated above for the patients with fibromyalgia.

All the subjects in the study were right-handed.

Assessment of autonomic function

A standard battery of non-invasive tests of autonomic function and heart rate variability (5 min duration) was used.

Prerecording procedure

The tests were performed in the morning between 9:30 and 11:30 a.m. The room temperature was maintained around 22–24°C. The laboratory was devoid of bright colors, sounds and bright light. The subjects were instructed to wear loose clothes, to take light breakfast 2 h before the test and refrain from tea, coffee or any other beverages in the morning. Each subject was requested to empty her urinary bladder before the start of the test. After reaching the laboratory, they were then asked to lie down quietly for 15 min before the commencement of the tests. Standard ECG limb electrodes were applied and a sphygmomanometer cuff was attached to the left arm for the recording of blood pressure.

Autonomic activity

Heart rate variability (HRV) was taken as a measure of autonomic activity (tone) and measured after the subjects had rested for 15 min. HRV recording and analysis was done using the Nevrokard software (version 6.4.0, Medistar, Slovenia) from a 5 min ECG recording. This consisted of a PCI 20450P DAS port A/D converter hardware apparatus (Intelligent Instrumentation, Tucson, AZ) that acquired and recorded the ECG. A signal sequence was recorded for 300 s. Power line noise was rejected by applying the 50 Hz hardware notch filter. The physiological signal was adaptively amplified by the data acquisition system (DAS) system for an accurate detection of the R-peaks. The ECG was sampled at 500 Hz [14]. Upon completion of the ECG acquisition, R-peaks were detected using the inbuilt adaptive fuzzy-R-peak detection tool of the Nevrokard. The ambiguities in the R-peak detection, if any, were minimized by visual inspection of the R-peak detections. Erroneous detections were ignored while missing beats were inserted prior to HRV analysis. Abnormal beats were identified and dealt with adequately, while recordings with a high number of ectopic beats were discarded from analysis. The normal-to-normal R–R interval was utilized to perform computation of HRV measures from time and frequency domains. In the time domain analysis SDNN, RMSDD, NN 50 count, and PNN50 count were selected for the statistical analysis. The spectral power density of the different component frequencies in the heart rate was carried out by the fast Fourier transform (FFT). The power spectrum can be divided into three frequency bands of very low frequency (VLF) 0.003–0.04 Hz, low frequency (LF) 0.04–0.15 Hz and high frequency (HF) 0.15–0.4 Hz [14].

Resting blood pressure and heart rate

Before starting the autonomic reactivity tests the resting autonomic parameters were measured which comprised of resting blood pressure and the resting heart rate.

Autonomic reactivity

For the assessment of sympathetic reactivity, blood pressure responses to lying to standing test, isometric exercise test and cold pressor test were measured. To assess the parasympathetic reactivity, heart rate responses to deep breathing test, Valsalva maneuver and lying to standing test were recorded. These tests have been described elsewhere [15]. Electrocardiogram and respiration were recorded using a polygraph which was a four channel POLYRITE-4 (Recorders and Medicare Systems, India). The main console had a switch for a chart drive to move the paper at varying speeds. Each channel had a driver amplifier and one pen-writing device. There was a separate channel for event marking, which could give pulses at a rate of 1 or 10 per second. For the hand grip test a light and small hand-grip dynamometer (Jetter and Scheerer, Germany) was used which had a scale in kilograms (0–250 kg) and a needle for showing the grip strength. For the Valsalva maneuver, a mercury manometer which was locally assembled in our laboratory was used. It consisted of a U-shaped graduated glass tube with bulb on one arm filled with mercury. On one end of the glass tube was connected to a mouth piece through rubber tube. The subjects were asked to increase the intrathoracic pressure after normal inspiration, by expiring forcefully into the mouthpiece connected to a mercury manometer, so as to raise the mercury level to 40 mmHg and maintained this for 15 s.

Statistical analysis

An SPSS 10 Statistics Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) was used for the analyses. Statistical analysis was done using unpaired Student's *t* test with two-tailed significance for the comparison of autonomic function of patient versus control group. Non-parametric tests (Mann–Whitney tests) were applied for the analysis of the heart rate variability. Normally distributed data were expressed as mean ± standard deviation (SD) and non-normally distributed data were expressed as median (minimum–maximum) values. A p value ≤ 0.05 was considered statistically significant.

Results

All the patients had confirmed primary fibromyalgia with mean duration of illness as 5.56 ± 3.05 years. The mean number of tender points among the patients was 11–18 (Mean ± S.D.: 15.16 ± 2.76 points; Median: 16 points). The anthropometric parameters between the fibromyalgia patients and controls with respect to age (39.95 ± 6.4 vs. 38.23 ± 5.7 years), height (153.93 ± 6.46 vs. 155.48 ± 6.17 cm) and body mass index (BMI) (25.97 ± 3.5 vs. 24.3 ± 5.17 kg/m^2) were statistically similar.

The fibromyalgia patients had a significantly higher systolic (116.76 ± 12.88 vs. 106.62 ± 9.61 mmHg; $p = 0.000$) and diastolic blood pressure (78.38 ± 10.02 vs. 71.05 ± 7.37 mmHg; $p = 0.000$) than the controls. Resting heart rate and respiratory rate were similar to controls.

The measure of total heart rate variability such as time domain parameters namely SDNN, SDSD, RMSDD, NN50 and pNN50 were significantly lower in the fibromyalgia patients than the controls (Table 1). Among the frequency domain parameters, the values for the HF% were

significantly lower in the fibromyalgia patients than the controls suggesting lower levels of parasympathetic drive at rest (Table 2).

The change in the blood pressure (delta) responses to the lying to standing test (fall in systolic blood pressure in 0.5th minute 10 ± 7.28 vs. 7.59 ± 5.54 mmHg), cold pressor test (rise in diastolic blood pressure in 1st minute 14.49 ± 8.67 vs. 14.49 ± 5.74 mmHg) and handgrip test (rise in diastolic blood pressure in 1st minute 7.86 ± 4.9 vs. 9.32 ± 5.7 mmHg) were not significantly different in the patient and control group.

Two patients could not perform the cold pressor test because of cold temperature induced severe pain in the upper limb. The fibromyalgia patients were not able to perform the handgrip test for the standard duration of 4 min with 30% force of maximum voluntary contractions (MVC). So the test was conducted with 50% force of the MVC for 1 min. The patients with fibromyalgia are not able to press the handgrip dynamometer effectively so something new needs to be designed in place of the existing dynamometer. It was difficult to measure blood pressure in 12 patients with fibromyalgia because of excessive pain and shaking of hand during hand grip test.

Parasympathetic reactivity measured as valsalva ratio (1.83 ± 0.49 vs. 1.73 ± 0.38); 30:15 ratio during lying to standing test (1.25 ± 0.26 vs. 1.27 ± 0.17); delta heart rate (19.31 ± 10.07 vs. 23.10 ± 8.5) and expiratory to inspiratory ratio (E:I) (1.29 ± 0.14 vs. 1.39 ± 0.31) during deep breathing test was comparable in both the groups.

Discussion

A widely accepted essence of the earlier studies is that the dysautonomia among the fibromyalgia patients is characterized by a tonically hyperactive sympathetic nervous system (at rest) which is hypo reactive to physical stress stimuli. However, these results are based on the basis of a few tests for the autonomic dysfunction. In the present study we assessed various components of autonomic nervous system in fibromyalgia patients using a comprehensive standard battery of non-invasive tests.

Autonomic abnormality has been documented in conditions closely allied to fibromyalgia syndrome such as irritable bowel syndrome (IBS), chronic fatigue syndrome and migraine headaches. The patients with chronic fatigue syndrome (CFS) demonstrate a dysautonomia with orthostatic intolerance similar to the postural orthostatic tachycardia syndrome (POTS) [16]. Likewise patients with irritable bowel syndrome (IBS) show signs of increased sympathetic activity on spectral analysis and a flattened 24 h pattern of heart rate variability with significantly lower levels of vagal

Table 1 Time domain analysis of the fibromyalgia patients and controls

Parameters	Patients ($n = 42$)	Controls ($n = 42$)	p value
SDNN	24.2397 (7.75–83.15)	41.3836 (15.60–145.96)	0.002
SDSD	19.8184 (2.51–106.16)	31.7302 (10.46–187.95)	0.003
RMSDD	19.7940 (2.51–106.01)	31.6855 (10.45–187.67)	0.003
NN50	2 (0–107)	15 (0–131)	0.011
pNN50	0.5168 (0–30.31)	3.6985 (0–35.79)	0.008

A p value ≤ 0.05 is statistically significant. Values are expressed as median with (interquartile) range

SDNN standard deviation of all RR intervals, *SDSD* standard deviation of successive RR intervals, *RMSSD* root mean of squared successive RR Intervals, *NN50* number of RR intervals ≥ 50 ms, *pNN50* percentage of NN50

Table 2 Frequency domain analysis of the fibromyalgia patients and controls

Parameters	Patients ($n = 42$)	Controls ($n = 42$)	p value
LF power (n.u.)	45.8060 (7.3–86.58)	38.1160 (9.62–76.76)	NS
HF power (n.u.)	44.2180 (5.54–84.72)	52.064 (9.66–89.68)	NS
Total power	680.78 (86–4828.479)	927.93 (113.25–5741.61)	NS
LF%	26.47 (4.37–56.58)	27.38 (8.9–60.12)	NS
HF%	25.84 (3–68.28)	37.28 (9.05–85.4)	0.023
LF/HF	0.9789 (0.09–14.99)	0.8595 (0.11–4.52)	NS

A p value ≤ 0.05 is statistically significant. Values are expressed as median with (interquartile) range

LF low frequency, *HF* high frequency, *n.u.* normalized unit and represent the relative value of each power component in proportion to the total power minus the VLF component, *LF% and HF%* are the percentages of total power distributed to the LF and HF band, respectively, *LF/HF ratio* ratio of absolute LF to HF power (in ms^2)

tone during sleep as compared to healthy controls [17, 18]. These results suggest that systemic sympathovagal balance is shifted in the patients with IBS.

In our study the resting systolic and diastolic blood pressure is significantly higher in the patients with fibromyalgia as compared to the healthy controls. This finding is important especially because the blood pressures of our patients with fibromyalgia, though higher are within a normal clinical range and have only a statistically significant higher value. Our finding is in sync with the outcome of other studies that the patients with fibromyalgia have a higher vascular sympathetic tone [4, 5, 8].

A reduced vagally mediated variability in heart rate is present in the overall HRV over 24 h in patients with fibromyalgia in terms of SDNN, SDANN and pNN50 indices [4]. In our study the time domain measures are significantly lower in the fibromyalgia patients than the controls indicating lesser parasympathetic activity in case of patients (Table 1). The frequency domain analysis results in our study further substantiate these findings where a significantly lower high frequency percentage (HF%) is observed in the patients with fibromyalgia (Table 2). A low HF is also reported in patients with hypertension, sleep apnea and chronic fatigue syndrome [1]. In our study the low frequency LF power (n.u.) and LF/HF ratio in the patients with fibromyalgia shows a higher trend though they fail to reach a level of significance (Table 2).

We report that the absolute values for the diastolic blood pressure (cold pressor test and the hand grip test at the 1st minute) and systolic blood pressure (lying to standing test at 0.5th minute) are significantly different in the fibromyalgia patients and healthy controls. However, the rise in value of diastolic pressure from the baseline values (in 1 min of cold pressor test and the hand grip test) and fall in systolic blood pressure in 0.5 min (during lying to standing test) are comparable. Thus, fibromyalgia patients and controls in our study reveal a similar sympathetic reactivity which can be the result of a high baseline blood pressure. Bou-Holaigah et al. [19] found that during tilt table testing, 60% of patients with fibromyalgia exhibit an abnormal decrease in blood pressure compared with 0% of controls ($P < 0.001$) and all of the patients who tolerate the tilt-table test for >10 min report a worsening of pain symptoms, whereas control subjects remained asymptomatic.

In our study the fibromyalgia patients and the healthy controls do not differ in terms of the parasympathetic reactivity. Significant differences in high frequency values in the HRV analysis between groups are reported only at the 5th minute of inspiration–expiration test and Valsalva test [20]. We hypothesize that the patients with fibromyalgia have a normal vagal function.

The patients with fibromyalgia exhibit restricted mobility. The chronicity of widespread pain (in our study the mean duration of illness is 5.56 ± 3.05 years) results in nearly an inactivity or a restricted mobility among the patients. Therefore, we propose that deconditioning takes place in the patients with fibromyalgia, which may be a consequence of pain related physical inactivity and may lead to a high sympathetic and low parasympathetic tone as seen in fibromyalgia patients (Fig. 1). The deconditioned muscle is more prone to microtrauma and hence becomes painful at even a lower level of exertion [21] thus giving rise to a cascade of pain and autonomic dysfunction as proposed in our model. Deconditioning also affects the cardiorespiratory system and the peripheral circulation and may be visualized as a reversal of the conditioning which occurs as a result of physical training [22]. Increased sympathetic tone in the blood vessels results in generalized vasoconstriction and induces an increase in muscle tension and local vasoconstriction in the arterioles and precapillary sphincters in the fibromyalgic muscle and skin. As a consequence, there is imbalance between oxygen supply and demand, leading to ischaemia and pain [23]. It is plausible that a defect of either the sympathetic reflex arc or in vascular end organ is present in the fibromyalgia patients. The activity of the sympathetic reflex arc as measured by resting MSNA between fibromyalgia patients and controls does not differ and the MSNA responses to isometric

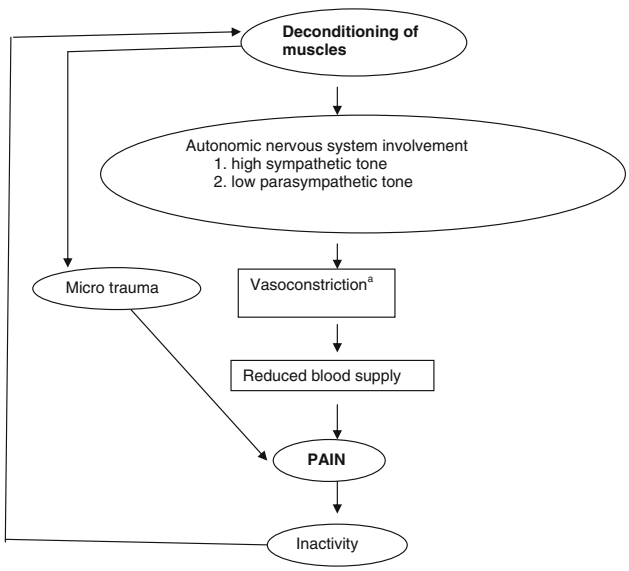

Fig. 1 A model proposing 'Deconditioning of muscles' leading to 'Autonomic dysfunction' as the key factor in the pathogenesis of pain in fibromyalgia: *1* The superscript *a* indicates that our study supports this link of the model proposed in an earlier study [23] which put forward a hypothetical model of pathogenic interactions of various factors that may be involved in fibromyalgia. *2* Deconditioned muscles are more prone to microtrauma resulting in a cascade of pain [21]. *3* Deconditioning also modulates the autonomic nervous system resulting in a high sympathetic tone and a low parasympathetic tone [22]. *4* A high sympathetic tone causes regional ischemia which in turn results in widespread pain, the hallmark of fibromyalgia

muscle contraction, post contraction ischemia or mental stress are not exaggerated in the fibromyalgia patients [24]. Thus, the sympathetic reflex arc is intact leaving the likelihood of the defects of vascular end organs which are continuously subjected to a persistently high blood pressure. Therefore, in our study the high vascular sympathetic tone (significantly higher baseline blood pressure in the fibromyalgia patients than in controls) does not necessarily reflect the cardiac sympathetic tone.

In the present study specific measures for studying deconditioning (e.g. physical performance in terms of cardiovascular fitness using bicycle ergometer etc.) could not be studied because of the study design and its limitations. Further studies for measuring cardiovascular sympathetic tone like blood pressure variability (BPV), baroreflex sensitivity (BRS) and noradrenaline spillover to substantiate our findings can be carried out. The question regarding the primary or secondary role of enhanced sympathetic activity in fibromyalgia and the risk of development of hypertension in the fibromyalgia patients as compared to healthy population can be answered by longitudinal studies. It is well established that different phases of the menstrual cycle affects the neurohumoral and the autonomic nervous system profile along with the number of tender points [25, 26] in fibromyalgia. Henceforth, more controlled studies should be carried out to look into the abovementioned limitations of the present study.

Conflict of interest No conflict of interest has been declared by the authors.

References

1. Martinez-Lavin M, Hermosillo AG (2000) Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. Semin Arthritis Rheum 29:197–199
2. Bengtsson A, Bengtsson M (1988) Regional sympathetic blockade in primary fibromyalgia. Pain 33(2):161–167
3. Martinez-Lavin M, Vidal M, Barbosa RE, Pineda C, Casanova JM, Nava A (2002) Norepinephrine-evoked pain in fibromyalgia. A randomized pilot study. BMC Musculoskelet Disord 3:2
4. Martínez-Lavín M, Hermosillo AG, Rosas M, Soto ME (1998) Circadian studies of autonomic nervous balance in patients with fibromyalgia: a heart rate variability analysis. Arthritis Rheum 41(11):1966–1971
5. Martínez-Lavín M, Hermosillo AG, Mendoza C, Ortiz R, Cajigas JC, Pineda C, Nava A, Vallejo M (1997) Orthostatic sympathetic derangement in subjects with fibromyalgia. J Rheumatol 24(4): 714–718
6. Vaerøy H, Qiao ZG, Mørkrid L, Førre O (1989) Altered sympathetic nervous system response in patients with fibromyalgia (fibrositis syndrome). J Rheumatol 16(11):1460–1465
7. Qiao ZG, Vaerøy H, Mørkrid L (1991) Electrodermal and microcirculatory activity in patients with fibromyalgia during baseline, acoustic stimulation and cold pressor tests. J Rheumatol 18(9): 1383–1389
8. Raj SR, Brouillard D, Simpson CS, Hopman WM, Abdollah H (2000) Dysautonomia among patients with fibromyalgia: a noninvasive assessment. J Rheumatol 27(11):2660–2665
9. Naschitz JE, Rozenbaum M, Fields MC, Enis S, Manor H, Dreyfuss D, Peck S, Peck ER, Babich JP, Mintz EP, Sabo E, Slobodin G, Rosner I (2005) Cardiovascular reactivity in fibromyalgia: evidence for pathogenic heterogeneity. J Rheumatol 32(2):335–339
10. Bennett RM, Clark SR, Campbell SM, Ingram SB, Burckhardt CS, Nelson DL, Porter JM (1991) Symptoms of Reynaud's syndrome in patients with fibromyalgia. A study utilizing the Nielsen test, digital photoplethysmography, and measurements of platelet alpha 2-adrenergic receptors. Arthritis Rheum 34(3):264–269
11. Lapossy E, Gasser P, Hrycaj P, Dubler B, Samborski W, Muller W (1994) Cold-induced vasospasm in patients with fibromyalgia and chronic low back pain in comparison to healthy subjects. Clin Rheumatol 13(3):442–445
12. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P et al (1990) The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 33(2):160–172
13. Wolfe F, Ross K, Anderson J, Russell IJ, Herert L (1995) The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 38:19–28
14. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation 93(5):1043–1065
15. Sharma RK, Deepak KK, Bijlani RL, Rao PS (2004) Short-term physical training alters cardiovascular autonomic response amplitude and latencies. Indian J Physiol Pharmacol 48(2):65–73
16. Stewart JM (2000) Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. Pediatr Res 48(2):218–226
17. Karling P, Nyhlin H, Wiklund U, Sjöberg M, Olofsson BO, Bjerle P (1998) Spectral analysis of heart rate variability in patients with irritable bowel syndrome. Scand J Gastroenterol 33(6):572–576
18. Heitkemper M, Burr RL, Jarrett M, Hertig V, Lustyk MK, Bond EF (1998) Evidence for autonomic nervous system imbalance in women with irritable bowel syndrome. Dig Dis Sci 43(9):2093–2098
19. Bou-Holaigah I, Calkins H, Flynn JA, Tunin C, Chang HC, Kan JS, Rowe PC (1997) Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia. Clin Exp Rheumatol 15(3):239–246
20. Doğru MT, Aydın G, Tosun A, Keleş I, Güneri M, Arslan A, Ebinç H, Orkun S (2009) Correlations between autonomic dysfunction and circadian changes and arrhythmia prevalence in women with fibromyalgia syndrome. Anadolu Kardiyol Derg 9:110–117
21. Bennett RM (1989) Beyond fibromyalgia: ideas on etiology and treatment. J Rheumatol 16(suppl 19):185–191
22. Scheuer J, Tipton CM (1977) Cardiovascular adaptations to physical training. Annu Rev Physiol 39:221–251
23. Jeschonneck M, Grohmann G, Hein G, Sprott H (2000) Abnormal microcirculation and temperature in skin above tender points in patients with fibromyalgia. Rheumatology 39:917–921
24. Elam M, Johansson G, Wallin G (1992) Do patients with primary fibromyalgia have an altered muscle sympathetic nerve activity? Pain 48:371–375
25. Hapidou EG, Rollman GB (1998) Menstrual cycle modulation of tender points. Pain 77:151–161
26. Hirshoren N, Tzoran I, Makrienko I, Edoute Y, Plawner MM, Itskovitz-Eldor J, Jacob G (2002) Menstrual cycle effects on the neurohumoral and autonomic nervous systems regulating the cardiovascular system. J Clin Endocrinol Metab 87(4):1569–1575