

Abstract

Fibromyalgia (FM) is a chronic pain syndrome often accompanied by an autonomic dysfunction. Reduced heart rate variability (HRV) indicating an enhanced sympathetic drive at rest and a lack of sympathetic reactivity during stress is commonly seen in subjects with FM. Earlier studies have shown that aerobic exercise can increase HRV in healthy persons. The aim of this study was to use recordings of HRV and blood pressure (BP) in the evaluation of the effects of a moderate intensity aerobic exercise program on autonomic functioning and pain in FM patients.

Twenty four women with FM and 25 female controls matched for age and physical activity were recruited for the exercise intervention consisting of 45- 55 min sessions 2 times per week for 12 consecutive weeks. HRV and BP were measured in all subjects during supine rest and in response to a tilt table test i.e. sympathetic reactivity. Pressure point threshold (PPT) was measured using an algometer. All recordings were conducted both at baseline and at post- test.

No group differences were found for resting HRV at baseline, but women with FM displayed a higher diastolic BP ($P=0.01$) than controls. Women with FM did also display a lower increase in diastolic BP than controls following tilt at baseline ($P=0.007$). There were no group differences in terms of sympathetic reactivity at baseline. Neither of the groups displayed changes in resting HRV from pre- to post- test. Women with FM displayed a decrease in resting BP from pre- to post- test (systolic BP: $P=0.01$, diastolic BP: $P=0.02$). Neither of the groups changed their sympathetic reactivity from pre- post- test (measured in HR and BP). No changes were seen in pressure pain threshold in neither of the groups.

This study did find differences in terms of BP between FM patients and healthy controls at baseline. However, in contrast to earlier studies there are not found any differences in any of the measured HRV parameters between groups. Considering few intervention effect was found, there is also possible that the intervention was not of sufficient duration to generate evident changes in the measured parameters. These ambiguous results do anyhow make it difficult to draw any conclusive remarks. Further studies are needed to assess autonomic functioning in FM patients and to which extent aerobic exercise affects the autonomic system within these patients. Further research is also needed to evaluate whether or not aerobic exercise leads to pain relieve in FM patients.

Introduction

The American college of rheumatology defines Fibromyalgia (FM) as a chronic pain syndrome with widespread pain for a duration of more than three months, and reduced pressure pain threshold (PPT) at more than 11 out of 18 anatomically defined tender point sites (Wolfe et al., 1990). FM patients commonly also report other symptoms such as sleep disturbances, muscle stiffness, fatigue, headache and irritable bowel syndrome. The prevalence of FM seems to range from 0.5- 4% of the population in industrialized countries and the syndrome is more common among females than males (Wolfe et al., 1995). FM does also have a large impact on work participation, as 20- 50% of persons with this condition are only able to work few days a week, or cannot work at all (Wolfe et al., 1995). It is also seen that family members of people already diagnosed with FM display a higher risk of developing this condition themselves. This makes a genetic predisposition for FM very possible, and this is thought to interact with the environment in triggering initial FM symptoms (Buskila & Neumann, 2005; Clauw & Crofford, 2003). Considering FM is a condition that has such great impact on daily function of a large amount of individuals, it is of importance both to search for the specific mechanisms involved, and further to establish how to best treat these subjects.

In attempting to understand the FM syndrome, researchers have suggested several mechanisms as possible factors in the development and maintenance of symptoms related to FM. Both factors residing from the central nervous system (consisting of the brain and the spinal cord) and the peripheral nervous system (all the nerves in the body outside the CNS) have been suggested as possible causes of this syndrome. However, research the last years have come to strongly indicate that the pathological mechanism responsible is centrally located (Abeles et al., 2007; Clauw & Crofford, 2003). More specifically, it is suggested that the symptoms commonly experienced by FM patients is related to a dysfunction in the autonomic nervous system (ANS) (Cohen et al., 2001a; Cohen et al., 2001b; Dogru et al., 2009; Furlan et al., 2005 Martinez-Lavin, 2004; Martinez- Lavin et al., 1997; Martinez- Lavin et al., 1998; Martinez- Lavin & Hermosillo, 2000; Sarzi-Puttini et al., 2006). The ANS functions below the level of consciousness and innervates the smooth muscles, the cardiac muscle, and glands in the body. The ANS is continually making adjustments in response to changing needs, modulating bodily functions to maintain homeostasis. The ANS makes bodily adjustments by regulating its two

subsystems that work in opposition to each other. The sympathetic division promotes physiological responses under stress while the parasympathetic division aids relaxing functions. In case of danger, for example, the sympathetic division becomes dominating, providing improved alertness, increased heart rate (HR) and blood pressure (BP) and so on, while parasympathetic modulations calms the body down when the surroundings are more safe (Marieb & Hoehn, 2007).

To assess autonomic regulation in the human body, large assortments of techniques have been used. These include recordings of muscle sympathetic nerve activity, microcirculation, sympathetic skin response, palmar conductance, and heart rate variability (HRV) analysis (Cohen et al., 2001a; Cohen et al., 2001b; Martinez- Lavin et al., 1997; Martinez-Lavin et al., 1998). Analysis of HRV is a relatively new method that has had large technological progress the last couple of decades. There have in this period been developed new and more accurate methods of conducting these analyses, which have in turn resulted in an increase in the research of autonomic functioning in FM subjects. It has been established that elevated sympathetic activity is related to a decreased HRV while dominating parasympathetic activity increase HRV. BP measurements have also frequently been used, being a useful measure in the evaluation of autonomic functions (Malik, 1996).

Bengtsson & Bengtsson (1988) were among the first to suggest a link between FM and a dysfunction in the ANS. In their study they conducted regional sympathetic blockades of the upper extremity (by stellate ganglion blockade). FM patients experienced marked improvements in regional pain and number of tender- points (in contrast to the control group receiving a placebo injection). Bäckman and co- workers (1988) observed similar results conducting a sympathetic blockade, hypothesizing that the blockade would release tension in skeletal muscle. Additionally, studies using HRV have frequently found abnormalities in FM subjects at rest, indicated by a continuous elevated state of activation in the sympathetic nervous system and higher heart rate than in controls (Cohen et al., 2001a; Cohen et al., 2000; Furlan et al., 2005; Martinez-Lavin, et al., 1998). Additionally, circadian studies have revealed nocturnal sympathetic predominance in these patients (Dogru et al., 2009; Martinez-Lavin, et al., 1998). Martinez- Lavin and co- workers (1997) used HRV to assess autonomic functioning in FM subjects, and revealed a diminished sympathetic response to orthostatic stress (i.e. when

changing from supine to upright posture). This has later been confirmed by other studies (Cohen et al., 2001a; Dogru et al., 2009; Furlan et al., 2005). However, contradictory results have also been reported. Elam and co-workers (1992) reported no differences between FM patients and healthy controls in muscle sympathetic nerve activity during rest using microneurography to directly record the sympathetic activity from the peroneal nerve.

There has evidently been some controversy and opposing results regarding the role of the ANS in the FM syndrome. However, the majority of the research conducted in the latest years strongly indicates a sympathetic dysfunction as a common denominator in this patient group (Cohen et al., 2001a; Cohen et al., 2001b; Dogru et al., 2009; Furlan et al., 2005; Martinez-Lavin, 2004; Martinez-Lavin et al., 1997; Martinez-Lavin et al., 1998; Martinez-Lavin & Hermosillo, 2000; Sarzi-Puttini et al., 2006).

The treatment of FM commonly includes pharmacological treatment, physical exercise and educational programs (Clauw & Crofford, 2003; Goldenberg et al., 2004; Mannerkorpi & Henriksson, 2007). Physical exercise may have profound effects, and it is suggested that low to moderate intensity aerobic exercise with low impact is most beneficial for these patients and may improve symptoms and distress (Busch et al., 2007; Gowans et al., 2001; Mannerkorpi & Henriksson, 2007; Meyer & Lemley, 2000; van Santen et al., 2002). Studies have earlier found increased HRV following aerobic exercise in healthy women (Jurca et al., 2004), and an extensive review also found endurance athletes to have greater resting HRV than sedentary controls (Aubert et al., 2003), both of these supporting the use of aerobic exercise to improve ANS function. However, no studies have been found to investigate HRV changes in FM patients following an exercise intervention. The aim of this study was to evaluate the effect of 12 weeks of moderate intensity aerobic exercise on pain and autonomic functioning in FM patients. HRV and BP were assessed both during supine rest and in response to a stressor (i.e. tilt-table test). The hypothesis suggests aerobic exercise both to reduce pain and number of tender points and to improve ANS functioning in women with FM.

Materials and Methods

Participants

Twenty- four women with fibromyalgia and 25 healthy female controls, matched for age were included in this study. An attempt was also made to match cases and controls for physical activity level. Most of the patients were recruited from the local fibromyalgia- association in Trondheim and some were recruited through the local newspaper. Some of the controls were also recruited through the local newspaper and some of them were employees at the Norwegian University of Technology and Science (NTNU). Before inclusion, patients were required to meet the criteria for the diagnosis of fibromyalgia defined by the American college of rheumatology. Diagnosis of FM was confirmed by a clinical examination performed by a physician. Participants having any disease or condition that could possibly affect the ANS were excluded from the study. These criteria included high BP (>140/90), endocrine/ metabolic diseases, heart disease with reduced function, lung disease with reduced function, chronic nervous disease (e.g., Parkinson's disease and epilepsy), cerebrovascular disease (e.g., stroke, dementia), pregnancy and heavy psychological problems. All participants gave written informed consent to participate, and the study was approved by the Regional committee for Medical Research Ethics.

Pressure pain threshold and International Physical Activity Questionnaire

To measure state of pain in the patients, an algometer measuring PPT was used. The PPT device establishes absolute pressure at pain threshold, creating an objective measure. PPT was measured at 10 locations throughout the body, using a SOMEDIC algometer (Probesize: 1cm², slope: 40kPa/s). The locations included in the measurement were; occipit m., supraspinatus m., trapezius m., rectus femoris m. and quadriceps femoris tendon. Pressure readings were conducted on both left and right side of the body. The subject was informed to press a button when she perceived the pressure transitioning to pain.

All subjects also answered the short version of the International Physical Activity Questionnaire (IPAQ), to assess the amount of physical activity in the last 7 days. The IPAQ consist of questions regarding how long the subjects in sum spent in vigorous, moderate and light

(walking) activities the last 7 days. The totals were calculated in METS (metabolic equivalents), a concept that determines energy expenditure from duration and intensity of the physical activity of the subjects.

Electrocardiography and blood pressure recordings

A total of three electrodes were attached to the subject for the electrocardiography (ECG) measurements. The surface area was first cleansed by rubbing the skin with red spirit- induced cotton. One electrode was then attached beneath the right collarbone (2nd intercostals space to the right of sternum) and the other electrode was placed between the 4th and 5th left costa (the left axillary line in the 5th intercostals space). The reference electrode was placed on the left side of the 7th cervical vertebrae (C7). Thereafter, a belt (strain gauge) was placed around the waist for respiratory measurements, and an accelerometer was attached to the upper part of the bench with the purpose of detecting the exact time the tilt was being conducted. The blood pressure measuring device (Gamma XXL LF) was then attached to the left upper arm, and the subject was instructed to lie down on the bench for the procedure to begin.

Experimental protocol

Before initiation of the test, subjects were given information regarding the experimental procedure, including the time aspects and the different types of measurement. The subjects also answered a questionnaire regarding sleep quality, time since last meal, coffee consumption the same day, illness the last week and cigarettes smoked the same day. To minimize possible interrupting factors from the environment, the lights were dimmed and the room was quiet. The temperature was also kept constant at a pleasant 25 °C. Subjects rested quietly in supine position, and were in advance instructed to stay awake during the test.

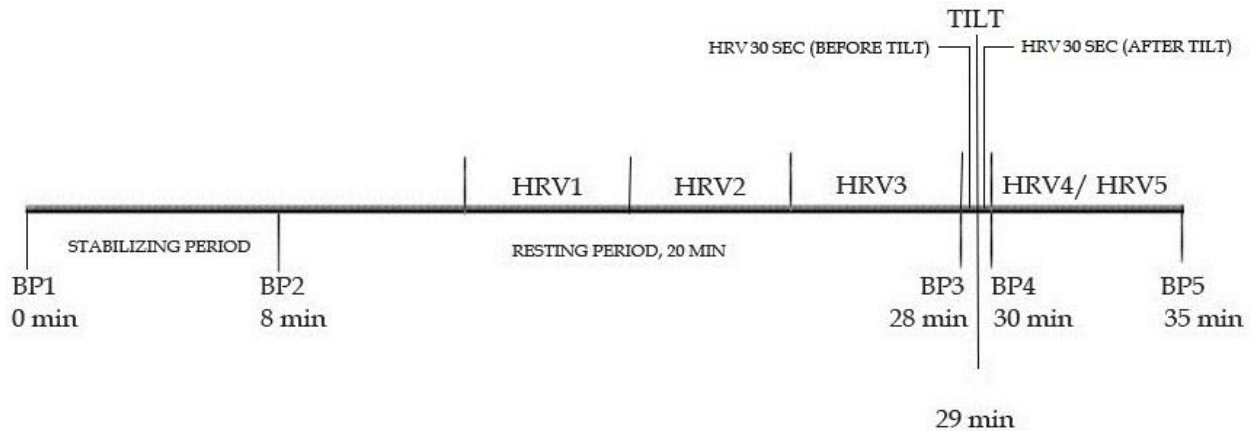


Figure 1 – Timeline showing BP- measurements and HRV intervals during the physiological recordings.

Figure 1 is an illustration of the measurements taking place during the 35 min recording of HRV and BP. BP was manually measured at the beginning (0 min), after 8 min, 28 min (before tilt) and at 30 min (at approximately 30 sec after tilt), and then again at the end of the session at 35 min. Between the third and fourth BP measurements (at approximately 29 min), the upper half of the table was manually rotated upwards to about 60°, leading to a sitting position. All measurements were conducted both at pre- and post- test.

Recording and analysis.

The ECG data were recorded using Delsys Myomonitor IV, and the recordings were conducted with a sampling frequency of 1000 Hz. Analysis of the recorded ECG data was performed using the computer software program Lab Chart Pro v. 7.0.3 (AD Instruments, UK). During the analysis, the recordings were split into 5 min segments (Figure 1). Three consecutive analysis (each of 5 min duration) was conducted before the tilt, and 2 overlapping 5 min recordings after the tilt (one starting at the end of tilt, and the second starting 1 min after tilt). Two shorter intervals (30 sec each) were also analyzed, whereas the first interval was recorded in the 30 sec prior to tilt, and the second interval started immediately after tilt. As these recordings only lasted for 30 sec, only HR and BP could be extracted.

All recordings were manually inspected and corrected for disturbances. Artefacts and ectopic beats were excluded from the analysis. Various measures of HRV were calculated, including time- domain analysis and frequency- domain analysis. The measurements included in the frequency domain analysis consist of high frequency power (HF) (0,15- 0,4 Hz), low frequency power (LF) (0,04- 0,15 Hz), and the LF/HF ratio. These frequency measures are based on rate of change in R-R length, and detect different aspects of ANS functioning in the subjects. A rise in the HF spectrum mainly reflects increase in parasympathetic activity. However, mediations in the LF spectrum are more unclear and are thought to reflect both parasympathetic and sympathetic activity (Cevese et al., 2001; Malik, 1996). The ratio of low-to-high frequency spectra power (LF/HF) is considered a measure of sympathetic activity (Malik, 1996).

In the time- domain, the extracted HRV variables include SDNN (standard deviation of the N-N interval), pNN50 (the percentage of consecutive RR-interval that differs more than 50 ms) and mean (HR) (Malik, 1996; Stein et al., 1994). SDNN reflects all the long- term components in the recording, thereby measuring sympathetic activity. pNN50 reflect short- time changes in HRV, and measure parasympathetically mediated alterations (Malik, 1996; Sztajzel, 2004).

Exercise intervention

The aerobic exercise program consisted of stationary cycling two times per week and patients and controls followed the same exercise protocol and in mixed groups. The duration of the intervention was 12 weeks. Each session was lead by an instructor and lasted 45- 55 min. Based on pre- exercise measurements of aerobic capacity (to be reported separately in another master thesis), the exercise was set to low- moderate intensity, i.e., average intensity below the anaerobic threshold, but with short intervals at anaerobic threshold. All subjects wore a heart- rate monitor (Polar FS2c) to assist them exercise at the intended intensity.

Statistical analysis

Independent samples t- tests was used for comparison between the two groups in pre- and post-test for HR, HRV and BP. A paired t- test was used for all analysis within groups. All t- tests were performed two- tailed. A *P*- value of 0.05 was considered significant. All statistical analysis were performed using SPSS, Inc., Chicago IL (version 17.0) and Microsoft Office excel 2007. A Shapiro Wilk's test was used to test the normality of the HRV variables. Most variables were normal- distributed, and parametric tests were therefore used in the analysis.

Results

Demographics and compliance

Baseline demographic data of the subjects participating at both the pre- and post-test are presented in Table 1. Information about age, height, weight, and total daily energy expenditure were collected and compared between the two groups. Body mass index (BMI) was significantly higher in the FM-group than in the control- group ($P=0.036$).

Table 1. Baseline demographics of the women with FM and controls that completed the intervention. METS are shown as a total of the reported activity level in 7 days from the international physical activity questionnaire (IPAQ).

	FM (n=17)	Controls (n=20)	<i>P</i> *
Age	55.8 (± 6.8)	51.8 (± 8.3)	0.072
BMI	28.8 (± 4.1)	25.2 (± 3.5)	0.002**
Total METS	1964 (± 2062)	2993 (± 2944)	0.201
Height (cm)	165.1 (± 6.1)	167,9 (± 5.7)	0.104
Weight (kg)	78.7 (± 12.1)	71.1 (± 10.3)	0.022**

BMI, body mass index; METS, metabolic equivalents

Values are mean ± standard deviation (SD)

*Independent samples t- test

** $P<0.05$

There was an evident drop- out in the course of the intervention. Out of initially 25 patients and 24 controls to be included to the study, 17 patients and 20 controls completed the 12 weeks of exercise and participated at the post- test. Five patients dropped out because of health problems not related to the intervention, 1 dropped out because of personal reasons, and 2 dropped out because they felt a worsening of their FM symptoms as a result of the exercise.

Among the controls, 1 dropped out because of health problems not related to the intervention and 3 dropped out because of personal reasons. Compliance varied considerable among the subjects that completed the intervention; the average exercise participation were 69% (range 35 to 91%) among the patients and 81% (range 53 to 100%) among controls. Based on the large inter-individual variations in compliance a subgroup-analysis was also performed, comparing subjects with >75% compliance versus subjects <75% compliance.

Heart rate reactivity

Figure 2 shows heart-rate during the 30 sec immediately before tilt and the 30 sec immediately after tilt at pre- and post- test (A and B). Figure 2 also shows Δ -change (before- after tilt) in heart rate responses at pre- and post test (C and D). Only the FM group displayed a significant increase in heart rate at pre- ($P=0.037$) and post-test ($P<0.01$) in response to the tilt. However, Δ -change in heart rate did not differ between groups, neither at pre- or post- test ($P>0.59$ for all comparisons). The latter indicate similar HR reactivity within the two groups both at pre- and post- test. There were no change in Δ -HR from pre- to post- test in any of the groups ($P>0.06$ for all comparisons).

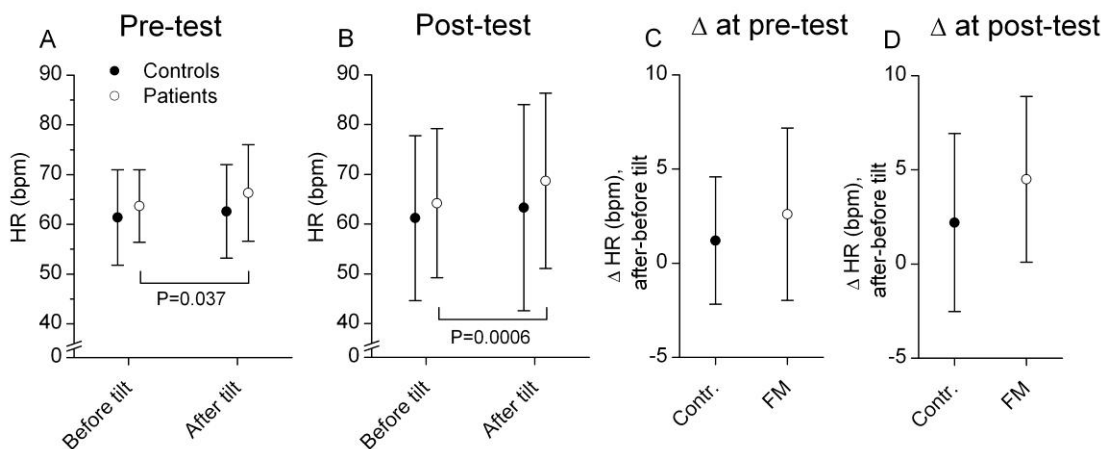


Figure 2. Heart rate 30 sec before and after tilt at pre- (A) and post- test (B), and Δ -change at pre- (C) and post- test (D).

Resting heart rate variability

Table 2 presents time- and frequency domain derived HRV variables for patients and controls during supine rest at pre- and post test. Subjects had lain relaxed in a supine position in approximately 20 min when this recording was conducted. Overall there was no difference between groups in any of the HRV variables, neither at pre- test ($P>0.29$ for all comparisons) or post- test ($P>0.14$ for all comparisons). There was no difference in HRV from pre- to post- test, neither within the FM group ($P>0.14$ for all comparisons) or within the control group ($P>0.17$ for all comparisons). This was also the case for the Δ - change from pre- post, which did not differ between the groups in any of the HRV variables ($P> 0.58$ for all comparisons).

Table 2. Heart rate variability during supine rest in patients and controls.

	FM	Cont.	P^*
Time domain			
HR pre	64.4±7.2	61.3± 9.57	0.29
HR post	65.7±6.9	61.5±9.0	0.14
P^{**}	0.85	0.41	
SDNN pre	48.6±26.0	52.7±19.2	0.60
SDNN post	51.6±26.0	53.3±23.8	0.84
P^{**}	0.91	0.42	
pNN50 pre	14.5±14.6	19±20.0	0.46
pNN50 post	12.3±11.7	15.8±19.6	0.54
P^{**}	0.25	0.25	
Frequency domain			
LF pre	46.5±17.3	48.7±17.9	0.71
LF post	52.0±16.1	53.8±17.1	0.76
P^{**}	0.17	0.30	
HF pre	49±16.5	47.1±17.5	0.74
HF post	41.9±13.8	43.2±16.5	0.80
P^{**}	0.30	0.14	
LF/HF pre	1.2±0.8	1.6±1.9	0.43
LF/HF post	1.5±0.9	1.7±1.3	0.66
P^{**}	0.95	0.33	

Values are mean ± SD

*Independent samples t-test

**Paired samples t- test

Blood pressure

Figure 3 shows BP measured 1 min before and 1 min after tilt (A-B, and E-F) as well as Δ -change in BP pre- and post-exercise (C-D and G-H). At the pre-test (before tilt), patients had significantly higher diastolic BP than controls ($P=0.01$). In the post-test there are no longer any BP- differences between the groups mainly due to reduced BP within the FM group. A reduction in BP within the FM group from pre- to post- test was evident both for systolic ($P=0.01$) and diastolic ($P=0.02$) BP before tilt, and for systolic ($P<0.01$) BP after tilt. Controls did not show any significant changes in BP from pre- to post-test, however controls displayed a larger systolic reactivity than controls at the pre-test ($P=0.007$). This difference was no longer present at the post-test. None of the two groups changes Δ BP from pre- to post- test.

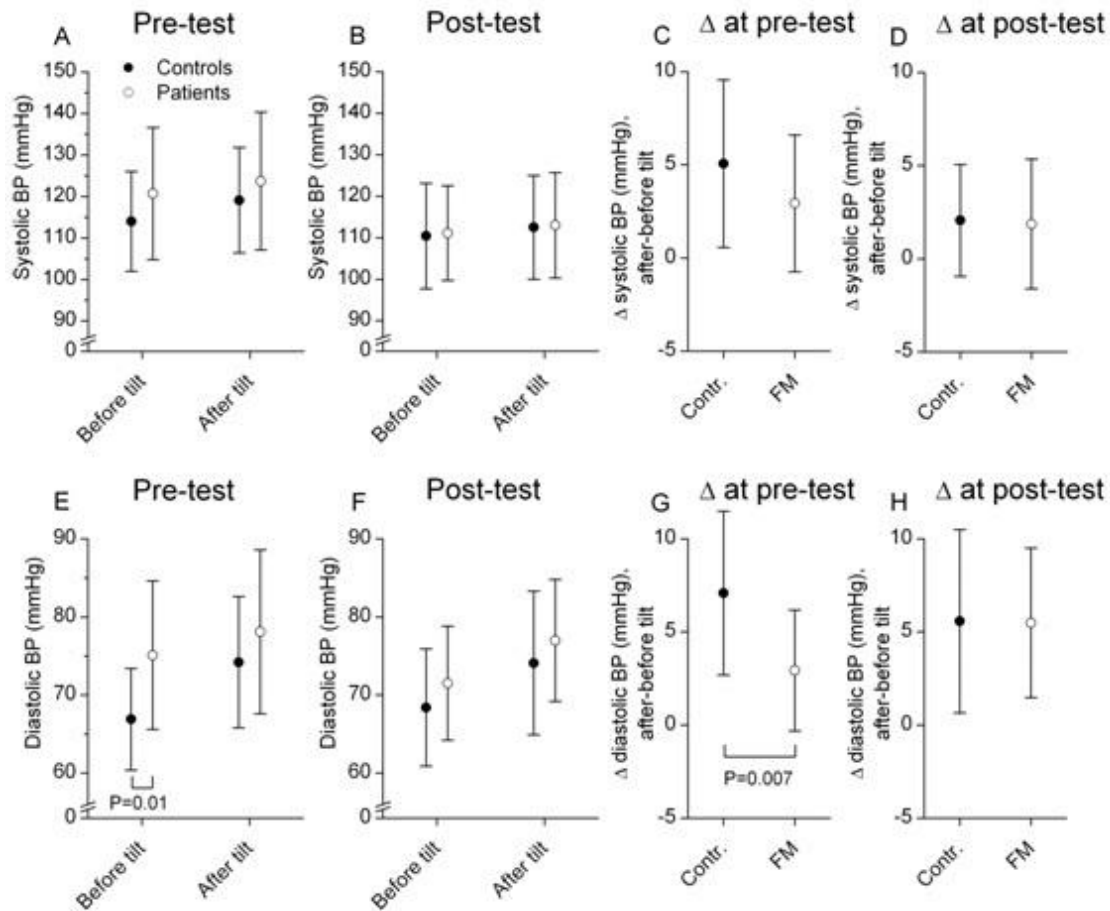


Figure 3. BP before and after tilt at pre- (A and E) and post- test (B and F), and Δ -change in BP from before to after tilt in pre- (C and G) and post- test (D and H).

Pressure pain threshold

Controls had significantly higher pain threshold at both pre- and post- test for all PPT sites ($P < 0.05$ for all comparisons) than patients. Table 3 shows PPT at pre- and post- test within the FM group. Although average PPT tended to increase for most PPT sites there was no significant change from pre- to post- test ($P > 0.06$ for all comparisons).

Table 3. Pressure pain threshold (PPT) at pre- and post-test within the FM group.

	FM		<i>P</i> *
	<i>Pre-test</i>	<i>Post-test</i>	
Occipit muscle (right)	204± 68	189±78	0.40
Supraspinatus muscle (right)	219±66	245±68	0.24
Trapezius muscle (right)	162±52	206±73	0.06
Occipit muscle (left)	156±51	170±56	0.22
Supraspinatus muscle (left)	211±94	228±84	0.57
Trapezius muscle (left)	159±54	184±58	0.08
Rectus femoris tendon (right)	382±202	371±165	0.77
Rectus femoris muscle (right)	340±181	366±163	0.49
Rectus femoris tendon (left)	337±176	381±180	0.16
Rectus femoris muscle (left)	347±156	408±208	0.09

Values are mean ± SD

*Paired samples t-test

Subgroups analysis

Since the subjects differed substantially in participation, a follow- up analysis was conducted where groups were split in to a high compliance- group (HC) and a low compliance group (LC) with a cutoff- point at 75% participation. These analyses then had 8 women with FM in each of the groups, and the controls then had 15 subjects in HC and 4 in LC. Groups were further tested for differences between patients and controls and from pre- test to post- test. There were also tested for differences between high/ low compliance groups. Tests were conducted comparing HRV recordings in the 5 min intervals before tilt, 30 sec HR and BP reactivity measurements, and at last for the PPT recording. None of these sub- analyses showed significant differences between high- compliance group and low- compliance group ($P > 0.05$ for all comparisons).

Discussion

This study examined the effect of 12 weeks of moderate aerobic exercise on autonomic function in women with fibromyalgia. No changes in any of the HRV (LF, HF, SDNN, LF/HF, pNN50) parameters were observed from pre- to post- test. Neither were there any differences between patients and healthy controls in any of the HRV variables. FM patients did however display higher resting BP than controls at baseline, and also lower Δ BP at baseline. These results were only evident for diastolic BP. Patients also displayed decreased BP during supine rest from pre- to post- test. There was no change in PPT from pre- to post- test within the FM group.

Heart rate and heart rate variability at supine rest (at baseline)

The findings in the current study are in line with the study by Martinez- Lavin and co- workers (1997), who also reported similar HR in women with FM and controls. However, most other studies have found FM patients to have significantly higher resting HR than controls (Cohen et al., 2001b; Cohen et al., 2000; Figueroa et al., 2008; Furlan et al., 2005). HR is mediated by the ANS and an increased HR in supine position indicates a more active sympathetic drive at rest (Malik, 1996). Reduced physical fitness may also relate to a higher resting HR, but unlike previous studies, cases and controls in this study were attempted matched on physical activity level.

No significant differences were observed between patients and healthy controls in any of the HRV parameters, neither in time- or frequency- domain. At baseline, patients did however display slightly lower values of pNN50, but slightly higher values of HF than controls. Both these parameters reflect parasympathetic activity and earlier studies have reported FM patients to have lower values in these parameters, thus suggesting a diminished parasympathetic state of activation, both in resting HRV (Cohen et al., 2001a; Cohen et al., 2000; Furlan et al., 2005) and as a total of 24- hours HRV measurements (Dogru et al., 2009).

The parameters for sympathetic activity, SDNN and LF/HF, were both slightly lowered within the FM group compared to the controls, though none of the findings reached significance. Earlier studies have mostly revealed opposite results i.e. elevated values of sympathetic activity in FM patients during rest (Cohen et al., 2001a; Cohen et al., 2000; Furlan et al., 2005) and as a

total of 24 hour recordings (Dogru et al., 2009; Martinez-Lavin et al., 1998). There were not observed any significant differences in LF activity, still FM patients had somewhat lower values than controls. Earlier studies have mainly found increased LF in FM patients (Cohen et al., 2000; Furlan et al., 2005), but the opposite have also been reported (Figueroa et al., 2008). Interpretation of LF power is also somewhat controversial because it is suggested by some to measure sympathetic modulation, and by others as measuring both sympathetic and parasympathetic influences (Malik, 1996).

Considering that earlier studies have not matched groups for physical activity level, the reduced physical activity in FM patients may have been a crucial factor in the differences experienced in HR and HRV in earlier studies. As shown in Table 1, the measured weekly energy expenditure from the IPAQ, were reported as approximately 2000 METS within the FM group, and approximately 3000 METS. Both groups are far beyond the minimum recommendations by the U.S. Department for Human Health Services (Leavitt, 2008), i.e., a minimum of 500-1000 METS a week is sufficient to achieve substantial health benefits for adults.

Intervention effect – heart rate and heart rate variability.

This study did not reveal any changes in any HRV parameters from pre- to post- test, neither in FM patients nor in controls. Accordingly there is no indication that 12 weeks of moderate aerobic exercise improve autonomic function in FM patients. A few studies have addressed somewhat similar issues earlier, and there have in these studies been reported unequal results. Figueroa and co- workers (2008) did find changes in some HRV parameters after 16 weeks of resistance training in women with FM. They found patients to display significant increases in total power and RMSSD (measure of parasympathetic modulation), but did not show any changes in sympathetic markers (LF power and LF/HF). However, the basis for comparison is weak, since there are fundamental differences between resistance exercise and aerobic exercise. Jurca and co- workers (2004) studied the effect of moderate intensity aerobic exercise on HRV in healthy, sedentary postmenopausal women exercising 3-4 times per week in an average of 44 min per session. Eighty- eight women were randomly assigned in an exercise group or control

group, and after 8 weeks of training the exercise group (n=49) significantly improved in all HRV measures compared to controls (n=39). Considering aerobic training lead to improved resting HRV in healthy women, this would also possibly apply to subjects with FM since the subjects enrolled to this study displayed the same trainability as the healthy controls. This is to be reported in another master thesis that was part of this project. The reason why none of the groups in our study experienced increases in any HRV variable, may possibly be a result of the exercise duration or/ and frequency. The amount of exercise may have been insufficient to produce measurable changes in the mechanisms related to autonomic function in the subjects participating in this study.

Blood pressure at supine rest (at baseline)

FM patients displayed significantly higher diastolic BP than controls at baseline. BP reflect changes in the internal system of the body, and varies in accordance with sympathetic/ parasympathetic drive, for example in response to vasodilation/ constriction and changes in cardiac output. In the same way as HR, an increased BP also indicates higher activity in the sympathetic nervous system (Marieb & Hoehn, 2007). These BP results contrast earlier studies which have not found any differences in BP between FM and controls at rest (Dogru et al., 2009; Elam et al., 1992; Figueroa et al., 2008). However, FM patients did have higher BMI than controls, which in turn is associated with higher BP (Dickinson et al., 2006).

Heart- rate and blood pressure in tilt- table test

The tilt table test creates a demand for increased blood- supply through causing a shift of blood flow from the thorax to the lower extremities. An auto- regulation normally occurs through the ANS, decreasing vagal tone and correspondingly increasing sympathetic tone to re- establish normal blood flow. The resulting rise in cardiac output (e.g increase in HR) leads also to an increase in BP. A passive tilt does also stress the sympathetic nervous system additionally because there are no muscle contractions to help increase venous return (Martinez-Lavin, 2007).

There were no differences between patients and controls in terms of HR reactivity, neither at pre- test nor at post- test. This is in line with earlier studies showing no difference between FM and controls in terms of the HR response to orthostatic stress. Martinez- Lavin and co- workers (1997) and Dogru and co- workers (2009) reported similar HR responses in FM and controls when subjected to active orthostatic stress (the subjects actively went from supine to standing position). Furlan and co- workers (2005) reported similar results using a tilt- table test up to 75°. It is still worth mentioning that even though these studies did not find differences in HR, they all found abnormalities in one or more of the HRV- parameters. However, the FM studies mentioned above used 5 min intervals for the tilt- test and therefore did not measure the instantaneous changes as in this study in which 30 sec intervals were used.

Significantly higher Δ BP (diastolic) were detected among controls than FM patients at pre- test, indicating a lack of sympathetic reactivity within the FM group. No difference were found in systolic BP. Earlier studies have not found any differences between FM patients and controls in BP in response orthostatic stress (Dogru et al., 2009, Furlan et al., 2005), but there have been found orthostatic intolerance indicated by a lack of increase in the LF spectrum (Martinez- Lavin et al., 1997; Furlan et al., 2005).

Extracting these short intervals were essential because the HR starts increasing after 1-3 sec after the onset of sympathetic stimulation, and takes about 30 sec to reach the steady state level (Berger et al., 1989; Wolf, 1997). Longer recordings will therefore not be as sensitive to the instantaneous response. The changes in HR and BP following tilt is in consent with earlier research, and both groups show moderate increases in these parameters that are in accordance with expected results for healthy individuals.

Intervention effect – Heart rate and blood pressure

Patients displayed a significant decrease in resting BP from pre- to post- test. Decreased BP is an expected effect of taking part in an aerobic exercise- regime, also for normotensive individuals (Whelton et al., 2002). The reason why a decrease in BP was not evident in controls may however originate in the fact that they displayed lower BP at baseline and therefore did not experience additional lowering of BP during the intervention

Neither patients nor controls displayed any changes in Δ HR or in Δ BP from pre- test to post- test. Both HR and BP are strongly associated with the ANS, and the results suggest that none of the groups changed their reactivity from pre- to post- test.

The reason why we did not find any changes in any of the groups may have its origin in the tilt- sequence applied in the current study. In opposition to earlier studies, only the upper body was involved in the tilt. This may generate a more moderate sympathetic response, leading to more subtle changes that are more difficult to distinguish. Further, a more moderate response would also require a larger sample size to detect changes.

Pressure pain threshold.

PPT was measured at six sites in the upper body, all classified as tender points in FM, and at four sites in the lower body (quadriceps femoris tendon and muscle at each side of the body) not considered as tender point sites. The results revealed a difference in PPT between FM and controls in the way that controls tolerated more pressure before perceiving pain. This is in accordance with earlier research, showing that FM patients have impaired PPT both in tender-points and in general (Busch et al., 2007). However this study is limited by that only 6 of the tender- points were measured, while earlier studies have measured all 18 tender- points.

None of the groups displayed significant changes in any of the sites tested after the 12 weeks of exercise. FM patients did have slight increases in PPT at 8 out of the 10 tested locations, though this was also the case for controls. Earlier research in this topic has displayed somewhat contrasting results. While Wigers and co- workers. (1996) found significant reduction in tender point tenderness in FM patients after an aerobic exercise intervention, but other studies found no significant changes in this measure (Busch et al., 2007; Gowans et al., 2001; Schachter et al., 2003). There is still lack of studies to give a conclusive answer to this question.

Sub- analysis

The sub- analysis was conducted to explore if the low compliance group had different changes than the high compliance group, and the possible relation between the differences. However, none of the results from the subgroup- analysis showed any differences in any of the measured parameters between those who had high versus low compliance. The groups were however quite small, making differences more difficult to reveal.

Limitations

There was a considerable drop- out rate both within cases and controls, which may lead to possible intervention- effects not being detected. However, no obvious trends were detected from pre- to post test, indicating that a larger sample- size may not have had affected the results. Also, the METS- scale used in this study may not be applicable for the general activity level in the subjects. The IPAQ (which the MET scores are extracted from) only considers activities the last 7 days, making it prone to not reflect a true long- term physical activity level of the involved subjects. Considering the questionnaire is self- administered, it is also possible that questions regarding physical activity may be perceived differently between subjects. Nevertheless, both groups are affected by these factors, meaning that the similarities observed between the groups may be true. Subjects with FM do however tend to experience fatigue as a result of their condition, making perceived intensity and thereby over- reporting of physical activity a possibility.

Conclusion

This study did not find women with FM to have any autonomic dysfunction compared to healthy controls at in any of the HRV parameters at baseline. This may be explained by the fact that both cases and controls in this study had the same physical activity level at the beginning of the intervention, and possibly therefore also had similar HRV. However, the BP measures indicated elevated sympathetic activity at rest and a lack of sympathetic reactivity when subjected to orthostatic stress. The fact that the exercise intervention did not give any indication of improved autonomic functioning or PPT may be a result of the frequency/ duration of the physical

exercise. Both groups reported well over the minimum METS- recommendations at baseline and the amount of exercise may not have been sufficient for evident autonomic changes to occur. It is still highly uncertain how autonomic function relates to aerobic exercise in FM patients, and further studies of longer duration are needed, both in the assessment of autonomic functioning within FM patients, and whether or not aerobic exercise leads to pain relieve in these subjects.

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