

# Resistance exercise training improves heart rate variability in women with fibromyalgia

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## Summary

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Fibromyalgia (FM) is characterized by generalized muscle pain, low muscle strength and autonomic dysfunction. Heart rate (HR) variability (HRV) is reduced in individuals with FM increasing their risk for cardiovascular morbidity and mortality. We tested the hypothesis that resistance exercise training (RET) improves HRV, baroreflex sensitivity (BRS) and muscle strength in women with FM. Women with FM ( $n = 10$ ) and healthy controls ( $n = 9$ ), aged 27–60 years, were compared at baseline. Only women with FM underwent supervised RET 2 days per week for 16 weeks. Baseline and post-training measurements included HRV and spontaneous baroreflex sensitivity (BRS, alpha index) from continuous electrocardiogram and blood pressure (BP) recorded with finger plethysmography during 5 min in the supine position. RR interval, total power, log transformed (Ln) squared root of the standard deviation of RR interval (RMSSD), low-frequency power and BRS were lower ( $P < 0.05$ ), and HR and pulse pressure were higher ( $P < 0.05$ ) in women with FM than in healthy controls. After RET, mean (SEM) total power increased ( $387 \pm 170 \text{ ms}^2$ ,  $P < 0.05$ ), RMSSD increased ( $0.18 \pm 0.08 \text{ Ln ms}$ ,  $P < 0.05$ ) and Ln of high-frequency power increased ( $0.54 \pm 0.27 \text{ Ln ms}^2$ ,  $P = 0.08$ ) in women with FM. Upper and lower body muscle strength increased by 63% and 49% ( $P < 0.001$ ), and pain perception decreased by 39% in women with FM. There were no changes in BRS, HR and BP after RET. Our study demonstrates that RET improves total power, cardiac parasympathetic tone, pain perception and muscle strength in women with FM who had autonomic dysfunction before the exercise programme.

## Introduction

Fibromyalgia (FM) is a chronic disorder characterized by generalized musculoskeletal pain, fatigue, reduced muscle strength and orthostatic intolerance (Olsen & Park, 1998; Cohen et al., 2000). Although the pathophysiology of FM is multifactorial, previous studies have suggested that autonomic dysfunction may be an important mechanism for pain and orthostatic intolerance in FM due to increased sympathetic-mediated vasoconstriction and baroreflex dysfunction (Martinez-Lavin et al., 1997; Cohen et al., 2000, 2001; Raj et al., 2000; Martinez-Lavin, 2004; Furlan et al., 2005).

Power spectrum analysis of heart rate (HR) variability (HRV) and baroreflex sensitivity (BRS) are non-invasive methods for evaluating the activity of the two divisions of the autonomic nervous system. HRV analyzes the beat-to-beat variation in R–R (RR) interval (Task Force, 1996), and BRS quantifies the capacity of the effective control of the sinus node (Cevese et al., 2001; Loimaala et al., 2003). Autonomic dysfunction has been evaluated by spectral analysis of HRV and BRS in individuals

with FM (Martinez-Lavin et al., 1997; Raj et al., 2000; Cohen et al., 2001; Furlan et al., 2005). It has been demonstrated that individuals with FM have reduced total power of HRV, vagal tone and BRS, and increased sympathetic activity (Martinez-Lavin et al., 1997; Raj et al., 2000; Cohen et al., 2001; Furlan et al., 2005). These neural abnormalities have been associated with greater risk of developing hypertension (Singh et al., 1998) and greater cardiovascular mortality (Tsuji et al., 1994, 1996; Huikuri et al., 1996; Singh et al., 1998).

A few studies (Jurca et al., 2004; Okazaki et al., 2005), but not all (Figueroa et al., 2007), have demonstrated improvements in resting HRV and BRS after 8–24 weeks of endurance exercise training. However, currently there is limited information about the effects of resistance exercise training (RET) on cardiac autonomic function. One study has suggested that HRV does not change after 8 weeks of RET (Cooke & Carter, 2005). Data from two longitudinal studies suggest that 12 weeks of RET either increase (Tatro et al., 1992) or do not affect BRS (Cooke & Carter, 2005) at rest in young healthy men.

It has been demonstrated that RET increases muscle strength and decreases pain perception after 12 and 21 weeks of RET in individuals with FM (Kingsley et al., 2005; Valkeinen et al., 2005, 2006). Considering that improvements in pain perception may be related with HRV, 16 weeks of RET may affect both pain perception and autonomic function. Therefore, the purpose of this study was to evaluate the effects of 16 weeks of moderate intensity RET on BRS and HRV in women with FM. We hypothesized that RET may improve cardiac autonomic modulation while increasing muscle strength in women with FM.

## Methods

### Subjects

Nineteen women aged 27–60 years, 10 with FM and 9 healthy controls were recruited from the Tallahassee metropolitan area through local newspaper advertisement and flyers. Women with FM had been suffering FM from 1 to 7 years. In the first visit, all potential subjects were screened by medical history questionnaires to evaluate inclusion and exclusion criteria. Exclusionary criteria included current smoking, blood pressure (BP) greater than 160/100 mm Hg, known diseases such as coronary artery, peripheral vascular, diabetes, renal, adrenal, pituitary and thyroid. Nine women with FM were excluded because they were smokers (4), or had cardiac arrhythmias (2), diabetes (1), and uncontrolled hypertension (2). Medications included the following: lipid-lowering (3), antidepressant (9), anti-inflammatory (2), estrogen-progesterone (5) and gastric antacid (4). None of the subjects participated in a structured exercise programme for more than 30 min daily and 3 days per week during the previous 6 months. All subjects gave written consent prior to their inclusion. The study protocol was approved by the Florida State University's Institutional Review Boards.

In the second visit for women with FM, our rheumatologist (V. M.) evaluated the number of active tender points and rated the sensitivity of the pain on a scale of 0 (no pain) to 3 (withdrawal of the patient from the examiner) of each tender point to determine the myalgic score. At least 11 out of the 18 specified tender points were required for eligibility to participate in the study (Wolfe et al., 1990). In the third visit for women with FM and second visit for healthy controls, subjects were tested after an overnight fast and refrained from caffeine, alcohol, and their prescribed medication for at least 12 h, and from vigorous physical activity for at least 24 h. Height and weight were taken and body mass index (BMI) was calculated. Thereafter, participants were required to rest in a quiet and temperature (25°C) controlled room in the supine position for a period of 20 min. Autonomic evaluation consisted of HR and BP measurements during 5 min. During the next two visits, each subject underwent maximal muscle dynamic strength test for the upper and lower body. Data were collected over a 2-week period. Only women with FM completed 16 weeks of supervised RET and post-training data were collected under the same conditions as they were measured at baseline.

### Autonomic measurements

Continuous electrocardiogram (ECG) and BP recordings were obtained from a modified CM5 lead sampled by a data acquisition system (Biopac, Santa Barbara, CA, USA) and from the left middle finger using a Finometer device (TNO Biomedical Instrumentation, Amsterdam, The Netherlands), respectively. The ECG and BP signals were sampled at a frequency of 1000 and 200 Hz, respectively, and stored on a computer for future analyses. Breathing was controlled using a metronome set at 12 breaths per min.

Both signals were manually inspected and sporadic ectopic beats and technical artefacts were linearly interpolated using the WinCPRS software (Absolute Aliens Oy, Turku, Finland). Fast Fourier transformation was used to obtain total power of HRV and its main components: high-frequency (HF, 0.15–0.4 Hz) and low-frequency (LF, 0.04–0.15 Hz) (Pagani et al., 1986; Task Force, 1996). Total power of HRV is an estimation of the global activity of the autonomic nervous system. The HF power is considered an indicator of cardiac parasympathetic activity (Pagani et al., 1986). The LF component of HRV is mediated by both sympathetic and parasympathetic activities (Task Force, 1996; Cevese et al., 2001). The LF/HF ratio of HRV has been proposed as cardiac sympathovagal activity balance. The time domain measure of HRV used in the present study was the square root of the mean squared differences of successive RR intervals (RMSSD) a marker of parasympathetic activity (Task Force, 1996).

We calculated spontaneous BRS using cross-spectral analysis of RR interval and systolic BP variability in the LF band. The  $\alpha$  index was used as measure of BRS if coherence was  $>0.5$  and the phase shift was negative (Pagani et al., 1988). Data acquisition and subsequent analysis were conducted following recommendations previously reported (Task Force, 1996).

### Strength testing

Maximal strength was assessed by the 1-repetition maximum (1-RM) test for the seated chest press and leg extension using variable resistance machines (MedX<sup>TM</sup>). Subjects were given a warm-up before testing. After at least 2 min of rest, subjects were progressed towards a maximal weight that could be moved one time through a full range of motion, the 1-RM. All measurements were recorded within 3–5 attempts. Following a minimum of 72 h, the subjects returned and the 1-RMs were verified. The highest measurement for the upper and lower body from the 2 days of testing was considered the 1-RM. The 1-RM test was repeated following 16 weeks of RET in women with FM.

### Exercise training programme

All FM subjects performed one set of 8–12 repetitions twice a week on nine exercises using MedX<sup>TM</sup> resistance machines: chest press, leg extension, leg curl, leg press, arm curl, seated dip,

overhead press, seated row and abdominal crunch. The lower back extension was completed with the subject's own body weight. Subjects began training at approximately 50% of their 1-RM and were slowly progressed throughout the 16 weeks to 80%. Once 12 repetitions were completed on two consecutive workouts with proper form, the weight was increased by 5–10 pounds for upper and lower body, respectively. The duration of each exercise session was approximately 30 min. Before and after each session subjects performed 5 min of warm-up and cool-down. Only women with FM went through RET.

### Statistical analysis

Natural log transformation (Ln) was used if the data were not normally distributed. Unpaired t-tests were used to assess group differences (FM versus control). In women with FM, differences between pre- and post-training data were compared using a paired Student's t test. Pearson correlations were used to estimate the association between RET-related changes in autonomic variables and myalgic score. All data are reported as mean  $\pm$  SD, except in figures (SEM). Significance was set at an alpha  $<0.05$ .

### Results

Participant characteristics are shown in Table 1. There were no significant differences in age, height, weight and BMI between the two groups. Maximal strength for the chest press and leg extension was significantly ( $P<0.05$ ) lower in women with FM. Resting autonomic and haemodynamic data are presented in Table 2. RR interval, total power, RMSSD, LF power and BRS were significantly ( $P<0.05$ ) lower in women with FM than in controls. HF power was also lower in the FM than in the control group, but it did not reach statistical significance ( $P = 0.08$ ). HR and pulse pressure were significantly ( $P<0.05$ ) higher in the FM than in the control group.

Ten of the original 15 subjects completed the RET programme; therefore, only 10 FM subjects were included in the statistical analysis. Although a woman developed a minor shoulder injury at week 10, she was able to complete the RET by doing unilateral instead of bilateral overhead press. There were no other adverse effects related to RET. Compliance to RET was

**Table 1** Subject characteristics.

Variable	Healthy controls	Fibromyalgia
Number	9	10
Age (years)	49 $\pm$ 8	50 $\pm$ 10
Height (m)	1.65 $\pm$ 0.04	1.64 $\pm$ 0.04
Weight (kg)	69.5 $\pm$ 11.7	75.3 $\pm$ 15.9
Body mass index (kg m <sup>-2</sup> )	25.6 $\pm$ 4.0	29.2 $\pm$ 5.8
Chest press strength (kg)	113.0 $\pm$ 24.8	74.8 $\pm$ 19.9*
Leg extension strength (kg)	130.2 $\pm$ 21.0	96.8 $\pm$ 15.0*

Values are expressed as mean  $\pm$  SD.

\* $P<0.01$  significant group difference.

**Table 2** Autonomic and haemodynamic measures in healthy controls and women with Fibromyalgia.

	Healthy controls (n = 9)	Fibromyalgia (n = 10)
RR interval (ms)	980 $\pm$ 113	849 $\pm$ 111*
Total power (ms <sup>2</sup> )	1966 $\pm$ 1340	869 $\pm$ 768*
RMSSD (Ln ms)	3.5 $\pm$ 0.5	2.9 $\pm$ 0.8*
Low-frequency (Ln ms <sup>2</sup> )	5.8 $\pm$ 1.1	4.2 $\pm$ 1.2*
High-frequency (Ln ms <sup>2</sup> )	6.2 $\pm$ 0.9	5.1 $\pm$ 1.6
LF/HF (Ln ratio)	0.95 $\pm$ 0.1	0.84 $\pm$ 0.1
BRS $\alpha$ (Ln ms mm Hg)	2.30 $\pm$ 0.50	1.49 $\pm$ 0.93*
Heart rate (beats min <sup>-1</sup> )	62 $\pm$ 7	72 $\pm$ 9*
Systolic BP (mm Hg)	116 $\pm$ 10	127 $\pm$ 15
Diastolic BP (mm Hg)	65 $\pm$ 5	65 $\pm$ 10
Pulse pressure (mm Hg)	51 $\pm$ 7	62 $\pm$ 11*

RMSSD, mean squared differences of successive RR intervals; Ln, natural logarithm; LF/HF, low-frequency/high-frequency; BRS, baroreflex sensitivity (alpha index); BP, blood pressure.

Values are expressed as mean  $\pm$  SD.

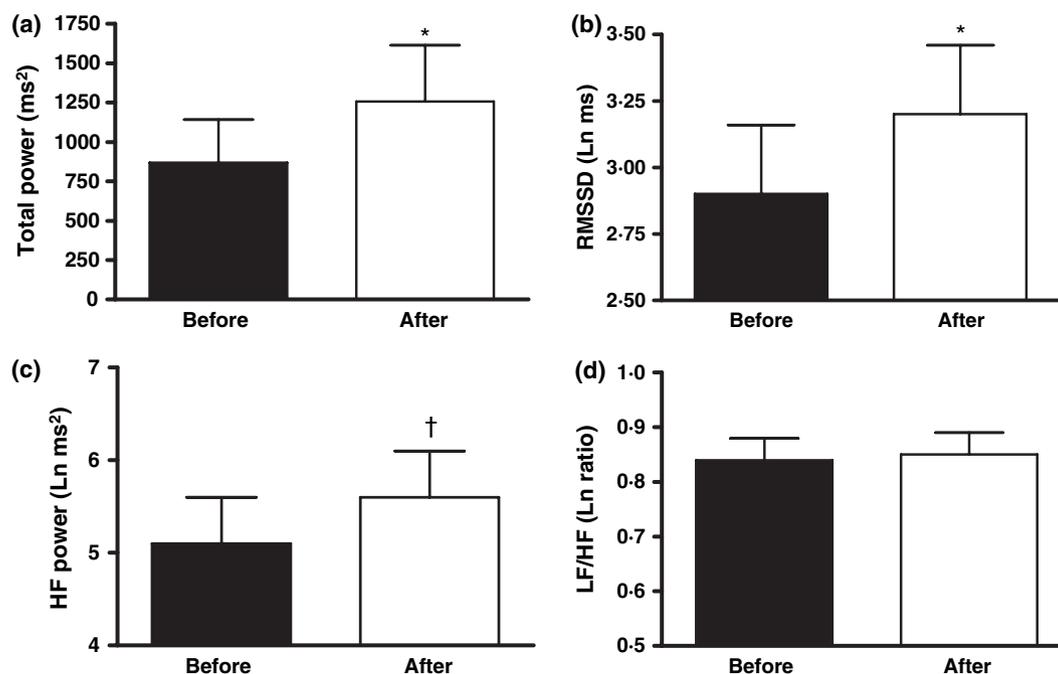
\* $P<0.05$ , significant group difference.

94  $\pm$  6%. As shown in Fig. 1, there were increases in total power ( $P<0.05$ ), RMSSD ( $P<0.05$ ) and HF power ( $P = 0.08$ ) with no significant change (2%) in the LF/HF ratio after 16 weeks of RET (Fig. 1). There were also increases in muscle strength for chest press of 45.5  $\pm$  22.4 kg (63  $\pm$  32%,  $P<0.001$ ) and leg extension of 46.8  $\pm$  17.2 kg (49.3  $\pm$  19.4%,  $P<0.001$ ) after RET in women with FM. The changes in RR interval (-1%), LF power (15%), BRS (5%), HR (2%), systolic BP (3%), diastolic BP (-1%) and pulse pressure (7%) after RET were not significant. Myalgic score decreased ( $P<0.05$ ) from baseline (15  $\pm$  3) to 16 weeks of RET (9  $\pm$  5). Changes in myalgic score were positively correlated with changes in total power ( $r = 0.76$ ,  $P = 0.01$ ) but not with other autonomic variables.

### Discussion

The main finding of this study was that a 16-week whole-body moderate intensity RET improved HRV (total power and RMSSD) and muscle strength in women with FM. In addition, our study confirms that women with FM have autonomic dysfunction characterized by attenuated parasympathetic and BRS at rest.

Our findings of low HRV and parasympathetic activity at rest in patients with FM agree with previous studies (Cohen et al., 2000, 2001; Furlan et al., 2005). Markers of parasympathetic activity in the frequency and time domain are the HF power and RMSSD, respectively (Pagani et al., 1986; Task Force, 1996). Our study showed a significantly reduced total power and RMSSD in women with FM when compared with healthy controls. In addition, reduced vagal activity accompanied a marked decrease in RR interval and consequent increase in HR in our women with FM. However, we did not find an increase in markers of



**Figure 1** Changes in total power (a), mean squared differences of successive RR intervals (RMSSD) (b), high-frequency (HF) power (c), and low-frequency/HF (LF/HF) and (d) before and after 16 weeks of resistance training in women with fibromyalgia. Values are mean  $\pm$  SEM. \* $P < 0.05$ ; † $P = 0.08$  versus before training.

sympathetic activity (LF power and LF/HF) as reported in previous studies (Cohen et al., 2000, 2001; Furlan et al., 2005).

Interpretation of LF power in absolute units as a marker of sympathetic activity is controversial because it is both sympathetically and parasympathetically mediated (Task Force, 1996). Several studies have demonstrated that a reduced LF power in the presence of low total power and HF power suggests a reduced cardiovascular tone in aging, physical inactivity, and hypertension (Pikkujamsa et al., 1998; Singh et al., 1998; Sevre et al., 2001; Okazaki et al., 2005). Therefore, an alternative interpretation of the lower LF power in our women with FM may represent a reduced vagal activity rather than an attenuated sympathetic activity. This assumption is supported by the lower RMSSD, a time-domain marker of parasympathetic activity, which has been found to be highly correlated with HF power (Task Force, 1996). The present study demonstrates an attenuated cardiac autonomic regulation in women with FM, which may increase the risk of hypertension (Lucini et al., 2002).

An improvement in HRV induced by endurance training is indicative of an enhanced cardiac parasympathetic control (Levy et al., 1998; Jurca et al., 2004). The novel finding of this study was that 16 weeks of supervised whole-body RET partially improved cardiac autonomic activity in women with FM. In agreement with a previous study in postmenopausal women (Jurca et al., 2004), we found an increase in total power and in RMSSD after training. Although our training programme increased the HF component of HRV, this change was not statistically significant ( $P = 0.08$ ). Because LF power is both

sympathetically and parasympathetically mediated (Task Force, 1996), the increase in total power in the present study may be attributed to the combined increase in parasympathetic activity in both the HF and the LF components of HRV, although the change was not significant in either individual component. In support to our finding of no change in sympathetic activity, previous studies have not found changes in resting catecholamine levels, normalized LF and LF/HF ratio following either resistance (Ryan et al., 1995) or endurance (Levy et al., 1998; Jurca et al., 2004; Figueroa et al., 2007) exercise training. Our results have important clinical implications because decreased HRV and parasympathetic activity are predictors of cardiac morbidity and mortality (Tsuji et al., 1994, 1996; Huikuri et al., 1996; Singh et al., 1998). Thus, improved HRV and parasympathetic tone with RET may reduce cardiovascular risk in women with FM.

In agreement with our findings, Cooke and Carter (Cooke & Carter, 2005) reported no change in both RR interval and HF power after 8 weeks of RET in young healthy individuals. In addition, Cooke et al. (Cooke et al., 2002) also found similar inconsistent effects on RR interval and a time domain index of parasympathetic activity (standard deviation of RR intervals) after 4 weeks of endurance training. It is difficult to provide an explanation for the lack of effect on the RR interval and HR in the presence of changes in total power and parasympathetic tone in the present study. Although it is expected that HR decreases parallel with enhanced cardiac parasympathetic activity after training (Jurca et al., 2004), we did not find changes in RR interval and HR despite adaptations in neural activity.

Importantly, our results disagree with a longitudinal study that reported no changes in HRV after RET (Cooke & Carter, 2005). A possible explanation for this discrepancy could be that our population was women with reduced physical activity who had autonomic dysfunction before the study.

Consistent with previous findings in other clinical populations (Kingwell et al., 1995; Kosch et al., 1999; Kim et al., 2007), women with FM had lower BRS and higher pulse pressure compared with healthy controls. Although BP was within normal limits in both groups, systolic BP was in the upper-normal range (prehypertension) in women with FM. It is well known that BRS is lower in hypertensive compared with normotensive individuals and this attenuation is more pronounced in women compared with men (Sevre et al., 2001). A suggested mechanism for the reduced BRS in patients with hypertension is increased large artery stiffness (Kingwell et al., 1995; Kosch et al., 1999), which reduces the mechanical deformation and stimulation of the baroreceptors.

Our finding differs from Furlan et al. (Furlan et al., 2005) who found similar baroreflex function in patients with FM and controls. This difference may be explained by the fact that subjects of this previous study (Furlan et al., 2005) had normal BP levels and alterations in autonomic markers of cardiac regulation are evident in the presence of prehypertension (Lucini et al., 2002), which was a characteristic of our FM group. Because increased pulse pressure is the strongest determinant of arterial stiffness (Kim et al., 2007), large artery stiffness may be implicated in the attenuated BRS in women with FM.

Only a few studies have evaluated the effect of RET on BRS (Tatro et al., 1992; Cooke & Carter, 2005). Using spontaneous BRS methods, Cooke et al. (Cooke & Carter, 2005) reported that 8 weeks of whole-body RET does not affect BRS in young men. Similarly, it has been reported that BRS does not change after moderate endurance exercise training (Iellamo et al., 2002). Since training-induced changes in BRS and sympathetic activity are inversely related (Iellamo et al., 2002), it is reasonable to assume that RET may not increase sympathetic control (Carter et al., 2003) by not affecting BRS (Cooke & Carter, 2005). Improvements in endothelial function (Olson et al., 2006) and BRS (Loimaala et al., 2003) have been found after 1 year of RET alone and combined with endurance exercise, suggesting that the beneficial effects of RET on vascular function and baroreflex-mediated control of heart rate may be associated and that these adaptations are observed with prolonged training periods. Our data may be of clinical relevance by demonstrating that moderate intensity RET does not alter BRS and pulse pressure, suggesting a lack of apparent deleterious neurovascular effect in women with FM.

Consistent with our findings, Valkeinen et al. (Valkeinen et al., 2006) found reduced pain perception after RET in postmenopausal women with a long history of FM symptoms, suggesting that duration of FM do not influence the effects of RET. In the present study, the increase in total power of HRV correlated significantly with the reduction in pain after RET. Zhang et al.

(Zhang et al., 2006) found that total power of HRV increased after relief of chronic pain with chiropractic care in postmenopausal women. Our findings suggest that RET has a beneficial effect on pain perception that may contribute to the improvement in cardiac autonomic function.

There are some limitations in the present study. The number of subjects in both groups was relatively small and there was no control group to compare the training effects. It could be argued that the wide age range (27–59 years) in the FM group may be a limitation due to the associations of age with autonomic dysfunction. However, total power of HRV declines after 20–30 years of age and remains stable to the age of 60 years with a gradual decline thereafter (Zhang, 2007). In the present study, only one woman with FM was young (27 years) and excluding her data from the analysis did not change the results. In addition, although some subjects were on vasoactive medications, they did not change medications or doses throughout the study and all of them abstained from their medications for at least 12 h before testing in an attempt to reduce the effects on autonomic function. Nonetheless, the present study shows favourable changes after short-term RET in previously sedentary women with FM, autonomic dysfunction and reduced muscle strength.

In conclusion, this study demonstrates that whole-body RET improves total power of HRV, parasympathetic activity, pain perception, and muscle strength in women with FM who had autonomic dysfunction prior to the intervention.

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