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Acute and Chronic Effects of Resistance Exercise on Autonomic Modulation and Vascular Function in Women with Fibromyalgia

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ACUTE AND CHRONIC EFFECTS OF RESISTANCE EXERCISE ON AUTONOMIC MODULATION AND VASCULAR FUNCTION IN WOMEN WITH FIBROMYALGIA

By

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I would like to dedicate my work to my mother, Georgia Kingsley. When I started my work with Fibromyalgia, I had no idea what it was, how to diagnose it, or how to treat it. Since then I have spearheaded 2 studies on Fibromyalgia and assisted on 2 others. I have learned about the disease from the existing literature and I have also contributed to it. I have also learned a great deal from the women that I have had the pleasure of working with through the years. With each woman that I have worked with, I have been reminded of what my mother suffers through each and every day. I have never forgotten why I was doing this work, and each study is more rewarding than the previous. This work is dedicated to an incredible woman that has preserved in pain with minimal hope of relief or help. I hope that I have assisted her in her plight, as well as all of the other women that have assisted me in reaching my goal. This is for you mom, I am forever indebted.

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ABSTRACT

Women with **Fibromyalgia (FM)** have agonizing chronic pain, reduced muscular strength and demonstrate autonomic and vascular dysfunction. Our prior work has demonstrated that exercise interventions improve the quality of life and reduce pain perception in women with FM. Furthermore, both acute and chronic resistance exercise have been to alter cardiac autonomic modulation in women with FM. The purpose of this dissertation was to gain a greater understanding of the influence of acute and chronic resistance exercise on cardiovascular function in women with FM. Therefore, the 3-part goal of the present study was to evaluate the acute and chronic effects of resistance exercise on: 1) the autonomic modulation, aortic wave reflection and BP**;** 2) the cardiovascular responses to sympathetic stimulation induced by the **cold pressor test (CPT)**; and 3) FBF and vasodilatory capacity in women with FM and HC.

Heart rate (HR), autonomic modulation, aortic pulse wave analysis and BP were determined at rest and during a 2-minute CPT administered before and after acute resistance exercise. Cardiac autonomic modulation was measured via **heart rate variability (HRV)** and was expressed in both frequency and time domains. Aortic pulse wave analysis was examined with the **aortic augmentation index (AIa**), the **aortic AIa normalized at 75 bpm (AIa@75)** and **reflection time of the arterial pressure wave (Tr).** BP measurements were taken using finger plethysmography. FBF and forearm vasodilatory capacity (reactive hyperemia) were measured using **venous occlusion plethysmography (VOP)** before and 15 min after acute resistance exercise.

Nine women with FM (42 ± 5 yrs; mean ± SD) and 15 HC (45 ± 5 yrs) underwent a battery of autonomic function tests before and after 12 weeks of RET. As has been demonstrated previously, the severity of FM as measured by the number of active tender points, myalgic score and the **Fibromyalgia Impact Questionnaire (FIQ)** was significantly ($p<0.05$) reduced in response to RET. Women with FM adapted to RET with increases in maximal strength that were similar to HC ($p<0.05$).

There were no significant effects of CPT on autonomic indices as measured by HRV. Prior to acute resistance exercise, the CPT significantly ($p<0.05$) increased HR, and altered autonomic function similarly in both groups before and after RET. There were no significant time effects of the post-exercise CPT on HR or autonomic modulation.

There were no significant effects of RET on HRV at rest or during recovery of resistance exercise. There were no group differences for the AIa and Tr during any condition or time. The post-exercise increased AIa with a greater magnitude compared to the pre-exercise CPT ($p<0.05$) at Pre2 and Post, but not at Pre1. Tr was lower during the post-exercise CPT compared to recovery before RET. There was no effect of resistance exercise or CPT on digital **systolic BP (SBP).** Digital **diastolic BP (DBP)** and the aortic DBP were significantly reduced ($p<0.05$) by the pre-exercise CPT, acute resistance exercise and the post-exercise CPT compared to rest before and after RET. Both aortic and digital **pulse pressures (PP)** were significantly increased ($p<0.05$) above rest during the pre-exercise CPT, recovery from resistance exercise and the post-exercise CPT before and after RET. However, aortic and digital **mean arterial pressures (MAP)** were significantly decreased ($p<0.05$) compared to rest during the pre-exercise CPT, recovery from resistance exercise and the post-exercise CPT at all time periods for each group. There were no group differences for vascular measurements at any condition and time point. Pre-exercise FBF increased significantly ($p<0.05$) after RET in women with FM (pre: 4.2 ± 2.7 vs. post: 8.3 ± 4.8 ml/min/100 ml of blood) and HC (pre: 3.2 ± 2.0 vs. post: 4.6 ± 3.1 ml/min/100 ml of blood). Post-exercise FBF increased significantly with RET in both groups of women (FM: +36.1% vs. HC: +29.5%; $p<0.05$). After RET, pre-exercise peak vasodilatory capacity increased in women with FM (Pre: 10.4 ± 4.6; Post: 19.2 ± 11.5 ml/min/100 ml of blood; $p<0.05$) and HC (pre: 9.7 ± 5.3; post: 13.5 ± 8.3 ml/min/100 ml of blood; $p<0.05$). Post-exercise peak vasodilatory capacity also increased significantly ($p<0.05$) in women with FM (+36%) and HC (+23.6%) after RET.

In summary, it was observed that FM patients generally exhibited normal autonomic responses to physical stress (CPT or acute exercise). Both HC and women with fibromyalgia adapted to RET with expected increases in maximal strength. In addition, RET increased maximal forearm vasodilatory capacity in both HC and in women with FM, while having minimal effects on autonomic tone. Nonetheless, it was observed that RET markedly decreased the severity of FM, effectively curing FM in some of these patients. It is concluded that RET reduces severity of FM without inducing major adaptations in autonomic function.

CHAPTER 1: INTRODUCTION

Fibromyalgia (FM) is an idiopathic rheumatological disease that affects roughly 7-10 million people in the United States (US) (144). Symptoms are diverse and include sleep disturbances (40), anxiety, depression (103), and reduced muscle strength and endurance (43). Diagnosis of FM is based on three pain characteristics: 1) pain for at least three months; 2) pain must be in all four quadrants of the body; and 3) pain upon moderate pressure of 11 out of 18 tender points (Figure 1) (146). Since these are the only criteria available, this may be why only 34% of those individuals with FM get appropriate diagnosis (17).

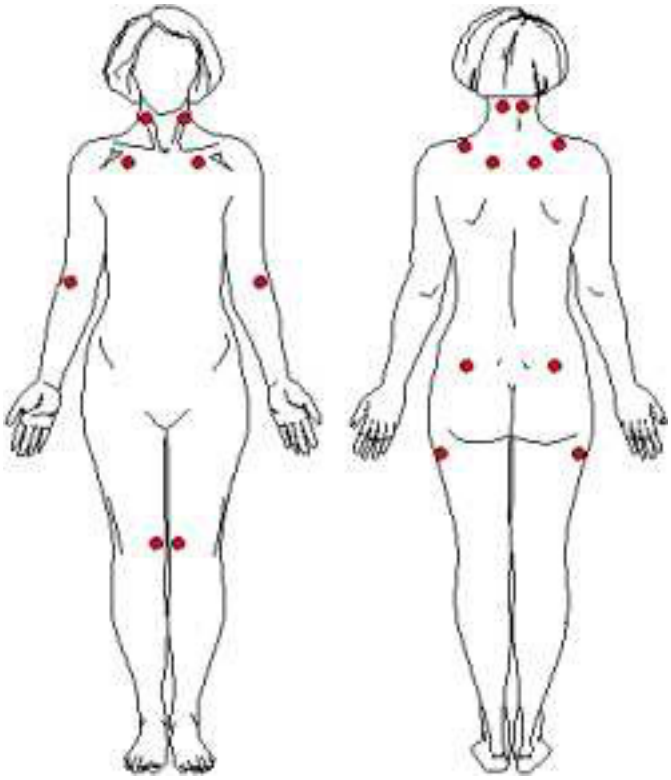


Figure 1. Diagnostic tender points in women with FM

Many women with FM tend to be overweight compared to healthy women. An increase in **body mass index (BMI)** increases the risk for cardiovascular complications. Sixty one-percent of those with FM are classified as overweight (BMI 25-29.9 kg/m^2) compared to 53% of

the healthy women in the US. However, Jones et al. (64) recently highlighted that there have been no interventions exclusively investigating overweight or obese women with FM.

Autonomic dysfunction contributes to a multitude of symptoms that are present in individuals with FM. Individuals with FM display hyperactivity of the sympathetic autonomic nervous system at rest (20) and an inability to increase sympathetic activity further during stressors such as cold exposure (120, 141) or standing (38, 95). **Heart rate variability (HRV)** measurements have emerged as powerful tools to examine the autonomic control of **heart rate (HR)** (2). The effects of resistance exercise on HRV are limited in healthy men and women (23, 54, 126) and are more limited in women with FM (36, 70)

Endothelial dysfunction may also assist in explaining the symptoms of FM (31, 68). Alterations in peripheral blood flow have been reported at rest in women with FM as well as during tests that stimulate sympathetic activity such as the **cold pressor test (CPT)** (120, 141). Endothelial dysfunction reduces arterial compliance and contributes to vasoconstriction (5) and increases **blood pressure (BP).**

A lack of standardized treatment further highlights how little is known about FM's etiology (128, 135). Currently, treatment for FM mainly relies on pharmacological and cognitive behavior therapy (119). Exercise interventions predominantly focus on endurance (aerobic) activity (44, 45, 66, 67, 99, 127, 130) with only a few studies investigating **resistance exercise training (RET)** (36, 48, 72, 116, 129). Studies that involve RET vary in duration, sets, repetitions, and intensity, making it difficult to compare data (65). These studies have shown improvements in maximal strength and endurance (49, 116), perceived pain (36, 48, 142) and self-efficacy (39) in women with FM but have done so without knowing the physiological mechanisms behind these changes.

Regular, moderate intensity aerobic exercise has been shown to increase **forearm blood flow (FBF)** and vasodilatory capacity (27) as well as to decrease aortic wave reflection (30) and BP (24, 56) at rest. The few studies that have investigated the vasodilatory response to RET using venous occlusion plethysmography have reported positive effects (3-5). The effects of RET on aortic wave reflection (11, 13, 25, 53) and BP (10, 12, 69) are mixed in healthy individuals. There are currently no studies investigating FBF, vasodilatory capacity or aortic wave reflection in women with FM.

Statement of the problem

The objective of this proposed study is to examine the acute and chronic effects of resistance exercise on autonomic modulation, aortic wave analysis, digital and aortic blood pressures, FBF and vasodilatory capacity in women with FM compared to **healthy controls (HC)** before and after 12 weeks of RET. In addition, the proposed study will determine the effects of RET on FM severity and maximal strength in women with FM.

Significance of the study

Data on the effect of acute and chronic resistance exercise are limited in women with FM**.** A lack of standardized treatment further highlights how little is known about FM's etiology (128, 135). Exercise interventions predominantly focus on endurance exercise with only a few studies investigating resistance exercise (36, 72, 116). Resistance exercise protocols vary in duration, sets, repetitions, and intensity, making it difficult to compare data across studies (65). The limited number of studies have found improvements in maximal strength and endurance (49), FM severity (36, 116) and self-efficacy (39) in women with FM but have done so without knowing the physiological mechanisms. Therefore, the present study will test the effects of resistance exercise on autonomic modulation and vascular function to evaluate their role on FM severity. The proposed experiments are important for several reasons:

- They will add to what is currently known about the effects of resistance exercise on autonomic modulation and vascular function in both healthy women and in women with FM.
- These studies will increase our knowledge on the association among autonomic modulation, vascular function and FM severity in women with FM.

Research Hypotheses

The following hypotheses will be tested:

Hypothesis 1: A reduction in muscular strength in women with FM contributes to an increase in disease severity. If so, then improvements in muscular strength will decrease FM severity. To test this hypothesis FM severity will be measured before and after 12 weeks of chronic resistance exercise in women with FM. If reductions in maximal strength contribute to increases in FM

severity then chronic resistance exercise will reduce the number of active tender points, the myalgic score and the FIQ in women with FM.

Prediction 1a: There will be increases in maximal muscular strength after RET in the women with FM and HC.

Prediction 1b: There will be decreases in the number of active tender points after RET in the women with FM as measured by a board-certified rheumatologist.

Prediction 1c: There will be decreases in the myalgic score after RET in the women with FM as measured by a board-certified rheumatologist.

Prediction 1d: There will be decreases in the FM impact after RET in women with FM as measured by the Fibromyalgia Impact Questionnaire.

Hypothesis 2: Women with FM have reduced autonomic modulation at rest and following a physiological stressor such as the cold pressor test or resistance exercise. Autonomic dysfunction results in increased BP and aortic wave reflection at rest and after a physiological stressor such as resistance exercise. Autonomic dysfunction can be improved via chronic resistance exercise. If so, RET will improve autonomic modulation, BP and aortic wave reflection at rest and after a physiological stressor in women with FM. To test this hypothesis autonomic modulation, BP and aortic wave reflection will be measured before and after acute resistance exercise prior to and following 12 weeks of RET in women with FM. If autonomic dysfunction increases BP and aortic wave reflection at rest and after acute resistance exercise then chronic resistance exercise will improve autonomic modulation, BP and aortic wave reflection at rest and after a physiological stress such as the cold pressor test or resistance exercise.

Prediction 2a: There will be sympathetic overactivity at rest in women with FM compared to HC as measured by HRV.

Prediction 2b: There will be increases in aortic BP and wave reflection at rest in women with FM compared to HC as measured by aortic wave analysis.

Prediction 2c: There will be increased central and peripheral BP at rest in women with FM compared to HC as measured by pulse wave analysis.

Prediction 2d: There will be no change in autonomic modulation in women with FM in response to CPT-stimulated cardiac autonomic modulation before and after acute resistance exercise prior to 12 weeks of RET compared to HC as measured via HRV.

Prediction 2e: There will be decreases in the responsiveness of aortic hemodynamics to CPT before and after acute resistance exercise prior to 12 weeks of RET compared to HC as measured via aortic wave analysis.

Prediction 2f: There will be no change in central and peripheral BP in response to CPT-mediated sympathetic vasoconstriction before and after an acute resistance exercise prior to RET in women with FM compared to HC as measured via pulse wave analysis.

Prediction 2g: There will be an improvement in autonomic modulation after 12 weeks of RET in women with FM in response to CPT-stimulated autonomic modulation compared to HC as measured via HRV.

Prediction 2h: There will be an improvement in the responses of aortic hemodynamics to CPT before and after an acute exercise following 12 weeks of RET in women with FM compared to HC as measured by aortic wave analysis.

Prediction 2i: There will be improvements in central and peripheral BP in response to CPT-mediated sympathetic vasoconstriction before and after acute resistance exercise after 12 weeks of RET in women with FM compared to HC as measured by aortic wave analysis.

Hypothesis 3: Women with FM have reductions in muscle blood flow. Resistance exercise training increases muscle blood flow. If so, then RET will increase blood flow in women with FM. To test this hypothesis FBF and vasodilatory capacity will be assessed before and after 12 weeks of RET. If blood flow is reduced in women with FM and RET increases blood flow, then 12 weeks of RET will increase FBF and vasodilatory capacity in women with FM.

Prediction 3a: There will be decreases in FBF and vasodilatory capacity at rest in women with FM compared to HC as measured by venous occlusion plethysmography.

Prediction 3b: There will be an improvement in the ability of women with FM to alter FBF and vasodilatory capacity after 12 weeks of RET compared to HC as measured by venous occlusion plethysmography.

Assumptions

For the purpose of this study, the following assumptions were made:

1. The participants will follow the testing procedures and exercise guidelines set forth by the researcher.

2. The participants will give their best efforts during testing and during every resistance exercise session.

3. All participants followed pre-test rules as they related to fasting, alcohol consumption, exercise, and medication.

4. During the control period participants will not change their activities over the 4-weeks.

Delimitations

The delimitations for this study included:

1. Nine women with FM and 20 HC between the ages of 35-50 years were recruited for the study. All women were premenopausal and were informed not to change their lifestyles during the duration of the study.

2. Participants were excluded if they had exercised within the past year, smoked within the past 6 months, hypothyroidism, history of cancer, any pituitary disease, vascular disease, severe depression, hypertension (≥160/100 mmHg), coronary artery disease, pregnant or contemplating pregnancy, diabetes, a BMI under 25 kg/m^2 or over 35 kg/m^2, taking any form of estrogen/progesterone, or taking any medications that alter cardiovascular function.

3. During the study participants were asked not to change their daily habits or to adopt any additional exercise programs outside of what was prescribed by the study. They were asked not to participate in or to begin any weight loss programs while participating in the study.

4. Participants underwent testing of FM severity, maximal strength, autonomic modulation and vascular function on 3 different occasions. This included measurements at baseline, following a 4-week control period and after 12 weeks of RET. Participants were classified as either diagnosed with FM or as HC.

Limitations

The researcher recognized the following limitations in the study's design:

1. The participants in this study were volunteers. Volunteers may bring with them a set of unique characteristics that may alter the internal validity of the results.

2. The participants in the study were to take their medications as needed except before some of the testing measurements.

3. The participants are limited to the Florida State University and surrounding Tallahassee area.
4. Participant age was limited to 35-50 years.

Definition of Terms

1-Repetition Maximum (1-RM) - The amount of weight that can be moved one time through a full range of motion (1).

Aortic Augmentation Index (AIa) – Defined as the differences between the first and second systolic peak divided by the pulse pressure and multiplied by 100. Calculated from the reflected wave to the primary arterial wave generated from ventricular ejection (109).

Cold Pressor Test (CPT) – A test in which the hand is submerged in cold, circulated water that stimulates sympathetic activity (12).

Fibromyalgia (FM) – An idiopathic disease that is characterized by pain upon pressure of 11 out 18 possible tender points (146).

Fibromyalgia Impact Questionnaire (FIQ) – A valid and reliable questionnaire to determine the impact of FM on week-to-week basis (9).

Heart Rate Variability (HRV) – A method to determine cardiac autonomic modulation through examination of variability from the peak of R wave to the next on an electrocardiogram (2).

High Frequency power (HF) – Indicative of vagal tone; expressed in absolute units (2).

Normalized high frequency (HFnu) – Indicative of vagal tone; expressed in normalized units (2).

Low Frequency (LF) – Indicative of sympathetic and parasympathetic modulation; expressed in absolute units (2).

Normalized low frequency (LFnu) - Indicative of sympathetic activity; expressed in normalized units (2).

Power Spectral Analysis (PSA) - Analysis of heart rate fluctuations which provides a noninvasive means of assessing the functioning of the short-term cardiovascular control mechanisms (2).

Reactive Hyperemia (RH) – An increase in blood flow following release of circulatory occlusion (55).

R-R Interval (RRI) – The time (in seconds) from the peak of one R wave to the next in an electrocardiogram (2).

CHAPTER 2: REVIEW OF LITERATURE

Background

Fibromyalgia is an idiopathic disease that is characterized by widespread, diffuse full body pain (146), reduced muscular strength and endurance (72, 117, 129), orthostatic intolerance (95, 122), reduced cold tolerance (120, 141) and fatigue (89, 117). While the etiology of FM is unknown, data suggest that autonomic dysfunction (19, 20, 36, 38, 93) and/or reductions in peripheral blood flow (31, 80, 98) may explain some of the symptoms. Studies that have evaluated autonomic function in women with FM, via HRV, have reported decreased vagal tone at rest (38) and an inability to alter sympathetic activity during a physiological stressor such as standing (38, 122). It has also been reported that women with FM have different sympathetic and vascular responses to the CPT (120, 141).

Treatment

Currently, treatment for FM mainly relies on pharmacological and cognitive behavior therapy (119). The use of drugs for pain suppression, muscle relaxation, sleep, irritable bowel syndrome, anxiety and depression are commonly used (26, 42, 139, 140). However, Sewitch and colleagues (134) have reported that roughly 50% of women with FM are non-adherent with their medication. Conservative methods such as physical therapy and cognitive training have also been used to treat persons with FM (42, 65). However, none of these modalities have been able to completely alleviate the symptoms in those that suffer from FM. An alternative treatment for those with FM has been exercise. Aerobic exercise has demonstrated better improvements in FM severity than pharmacological and conservative treatments (15, 43-45, 61, 65-67, 104, 119, 125). Even more recently RET has been shown to be beneficial for women with FM (36, 39, 48, 49, 72, 116, 129, 142). Those studies that have examined the responses to RET have demonstrated improvements in FM severity (36, 39, 116), maximal strength (48, 49, 72, 116, 129), and autonomic modulation (36).

Resistance Exercise on Fibromyalgia Severity and Maximal Strength

The majority of research utilizing exercise on women with FM has focused on aerobic exercise (43, 44). Resistance exercise was initially overlooked as a treatment modality because it was thought that FM was a disease of the skeletal musculature (15). However, recent evidence

has pointed to more central mediated mechanisms responsible for FM (19, 38, 92). Therefore, resistance exercise may be beneficial for this population.

Studies utilizing RET in women with FM have demonstrated increases in maximal strength (39, 45, 48-50, 72, 91, 116, 129, 142) as well as decreases in FM severity such as the number of active tender points (116, 142), the myalgic score (91, 116) and FM impact (116, 129). Increases in maximal strength in women with FM has been shown to be similar to HC (49). One of our earlier studies demonstrated that women with FM had significant improvements in upper body strength (7.7%) and lower body strength (20.6%) with a full body workout consisting of 10 resistance machines utilizing just 1 set of 8 to 12 repetitions being performed twice a week for 12 weeks (72). In this particular study, participants began training at 40% of their predetermined one repetition maximum (1-RM) and finished training at 80% of their 1-RM. In addition, a more recent study from our laboratory utilized a similar RET protocol over a period of 16 weeks in which participants began RET at 50% of their 1-RM. Increases in upper body strength and lower body strength were both over 30%. In a study by Hakkinen et al. (49) 21 weeks of RET increased maximal leg extension force similarly in women with FM and HC by 18% and 22%, respectively. These studies suggest that RET is not only tolerable, but also efficacious, for women with FM.

In an earlier study from our laboratory we assessed 12 weeks of RET on FM severity (72). We reported no significant changes in the number of active tender points, the myalgic score, or the FIQ after RET. Similar results were reported by Hakkinen et al. following 21 weeks of RET (49). However, a study by Valkeinen and colleagues did shown a reduction in the number of active tender points, 16.5 to 14.6 units, after 21 weeks of RET (142). Rooks (129) found a significant 28% reduction in FIQ score for the women with a combined aerobic and strength program. A more recent study from our laboratory (116), demonstrated that RET twice a week for 16 weeks was sufficient to decrease FM severity. Specifically, we published that 16 weeks of RET decreased the number of active tender points (14 to 10), the myalgic score (18 to 10 units) and the FIQ (60.3 to 45.8 units) (116).

Autonomic Modulation

Heart rate variability has emerged as a powerful tool to examine the fluctuations of the autonomic nervous system, which controls HR and BP (2). In the frequency domain,

measurement of HRV via power spectral analysis yields three distinct frequencies; low frequency (LF), high frequency (HF) and very-low frequency (VLF) (2, 88). Studies suggest that LF (0.04-0.15 Hz) power of HRV is indicative of parasympathetic/sympathetic balance and involves the arterial baroreceptors (19, 20, 79, 118). HF (0.15 -0.4 Hz) power of HRV is mainly under the control of the vagus and is rhythmic with ventilation (2). VLF (0.01-0.04 Hz) oscillations are not well defined physiologically (2, 20, 60). Power for each individual frequency is evaluated by examination of the total area under the curve for that component and may be expressed in absolute (ms^2) or normalized (nu) units (2). Normalized units are assessed by dividing the power of a component (HF or LF) by the total power, which has had the VLF removed, and then multiplying by 100 (2). The LFnu component, in conjunction with the LF/HF ratio, are indicators of cardiac sympathetic activity and sympathovagal balance (2, 18, 20). In the time domain, HRV yielded three distinct variables (2). Overall assessment of autonomic modulation was quantified using the standard deviation of the normal RR intervals (SDNN) (2). Vagal modulation was determined by the root mean squared difference of successive RR intervals (RMSSD) and the proportion of interval differences of successive RR intervals greater than 50 ms (pNN50 index) (2).

Autonomic modulation can easily be assessed noninvasively using HRV. Examples of tests that could be used to stimulate autonomic modulation include the tilt table test, the CPT or **isometric handgrip (IHG).** During autonomic stimulation a healthy individual will have a decrease in parasympathetic activity and an increase in sympathetic activity resulting in tachycardia and increased BP. On the contrary, women with FM may experience no change in parasympathetic/sympathetic activity during autonomic stimulation (38). Autonomic modulation in women with FM has been quantified during the tilt table test (38) and IHG (see preliminary data). Currently, no study has quantified autonomic modulation during the CPT in women with FM.

Autonomic dysfunction contributes to a multitude of symptoms that are present in individuals with FM (94). Individuals with FM display hyperactivity of the sympathetic ANS at rest (20) and an inability to increase sympathetic activity further during stressors such as cold exposure (120, 141) or standing (38, 95). Both Cohen et al. (20) and Furlan et al. (38) have reported greater levels of total power and LFnu concurrently with lower HFnu in women with FM compared to control women at rest. In addition, Figueroa and others (36) demonstrated that

women overweight with FM had a 126% reduction in total power and a 20% lower parasympathetic activity (RMSSD) compared to HC at rest. Women with FM demonstrated lower levels of Ln HF compared to HC, but it did not reach statistical significance (p=0.08). These alterations in HRV contributed to a significantly higher resting HR (13.9%) in women with FM compared to HC. In contrast to previous reports, there was no increase in sympathetic activity (LF power and LF/HF ratio) above HC in women with FM. In a more recent study, Kingsley et al. (70) demonstrated no differences in autonomic modulation between women with FM and HC.

Pilot data from our laboratory (71) have noted that the autonomic modulation measured via HRV is different between women with and without FM both at rest and during IHG (Figures 2 & 3). Autonomic modulation and BP data were collected in the seated position. Recordings were made during 2 minutes of rest and then followed by 2 minutes of IHG at 30% maximum voluntary contraction**.** These data demonstrate an altered autonomic control at rest demonstrated by reduced parasympathetic tone (HFnu) and increased sympathetic activity (LFnu) at rest. These data are consistent with other reports in that overweight women with FM have dysautonomia at rest and during a physiological stressor.

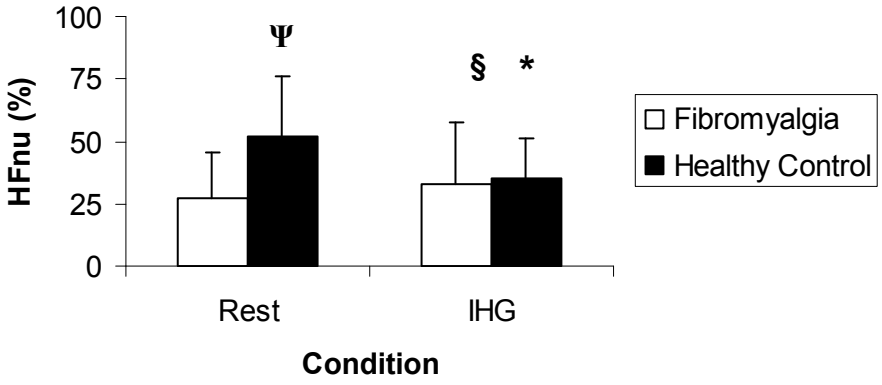


Figure 2. Differences in parasympathetic activity (HFnu) in women with FM (n=11) compared to HC (n=9) at rest and during IHG. There is a difference between the groups at rest (Ψp<0.05) and a group-by-time interaction (**§**p<0.05) due to a decrease in the HC (*p<0.05). Values are mean ± SD. (71)

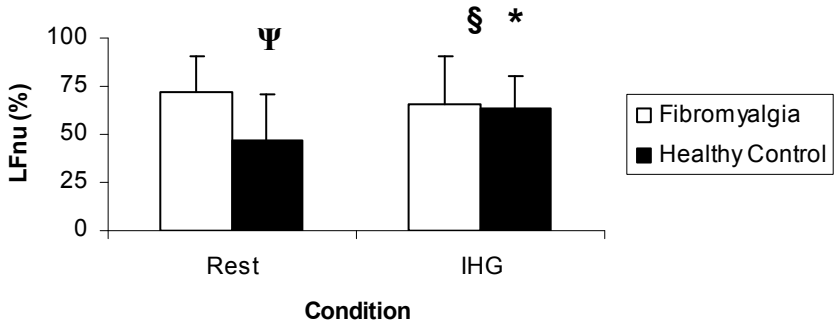


Figure 3. Differences in sympathetic activity (LFnu) in women with FM (n=11) compared to HC (n=9) at rest and during IHG. There is a difference between the groups at rest (Ψ $p<0.05$) and a group-by-time interaction (§$p<0.05$) due to an increase in the HC (*$p<0.05$). Values are mean ± SD. (71)

Reports investigating autonomic recovery from endurance exercise (35, 77, 87, 121) are more widespread than those using an acute bout of resistance exercise (54, 70, 126). Heffernan et al. (54) and Rezk et al. (126) both reported decreases in vagal activity after acute resistance exercise in young healthy men and women. Heffernan et al. (54) utilized the 10-RM on 8 exercises, and found a greater reduction in HF power after 25-35 min of an acute session compared to an aerobic exercise bout. Rezk et al. (126) assessed HRV between 15-90 min postexercise and demonstrated that vagal withdrawal (HFnu) persisted for 90 min postexercise after low- (40% 1RM) and high-intensity (80% 1RM) exercise. Conversely, Kingsley et al. (70) recently reported that acute resistance exercise consisting of 1 set of 12 repetitions (75% of the participants pre-determined 1-RM) of 11 exercises increased post-exercise vagal modulation (HFnu) in women with FM by 10.9% and reduced HFnu by 36.4% in HC. In addition, there was also a significant effect of the acute resistance exercise on post-exercise sympathetic activity (LFnu), such that women with FM displayed a 14.8% reduction, while HC had a 46% increase. Therefore, it is possible that the higher post-exercise HF power in women with FM is due to an attenuated vagal response during exercise that persists during the recovery.

In young healthy men and women there appears to be no change in HRV with RET (22). Cooke et al. showed that 8 weeks of RET did not change absolute or normalized values of HRV at rest. Collier et al. (21) investigated 4 weeks of RET on HRV in individuals that were borderline hypertensive, a manifestation of autonomic dysfunction. Collier et al. (21) reported

that RET had no effect on the Ln HF, Ln LF or the LF/HF ratio in the participants compared to 4 weeks of aerobic training. However, Figueroa et al. (36) demonstrated an increase in overall HRV following 16 weeks of RET in women with FM who had autonomic dysfunction prior to the intervention (36). Overall HRV was assessed via total power and parasympathetic tone (RMSSD). Women with FM demonstrated a 36% increase in total power as well as 12.3% increase in RMSSD after RET. Although not statistically significant ($p=0.08$) there was also an increase in HF power by 10.3% compared to before RET.

Aortic Wave Reflection and Blood Pressure

The aortic augmentation index (AIa) is considered a simple and noninvasive method to assess wave reflection. The AIa is calculated from the reflected wave to the primary arterial wave generated from ventricular ejection (Figure 4). In young individuals, the reflected wave returns to the aorta during diastole whereas in older individuals the wave amplitude is greater and the return occurs during systole due to increased arterial stiffness. An elevated AIa is a strong predictor of coronary heart disease (25) and has been linked to aging, hypertension, hypercholesterolemia, diabetes mellitus, and smoking (112).

The AIa is obtained from the analysis of the pressure waveforms recorded from the radial artery using applanation tonometry (111, 112). Flattening of the artery against the underlying bone records the pulse waveform significantly closer to those that are measured with a catheter (111). Through the use of a single, validated transfer function, an aortic waveform is generated from the radial waveform (110). The AIa is inversely related with height and heart rate (145), and is generally higher in women than in men (111). Arterial stiffness increases progressively with age (105). Aerobic exercise decreases the AIa in the healthy population due to increased arterial compliance or reduced stiffness, and thus decreasing risk factors for cardiovascular disease (137).

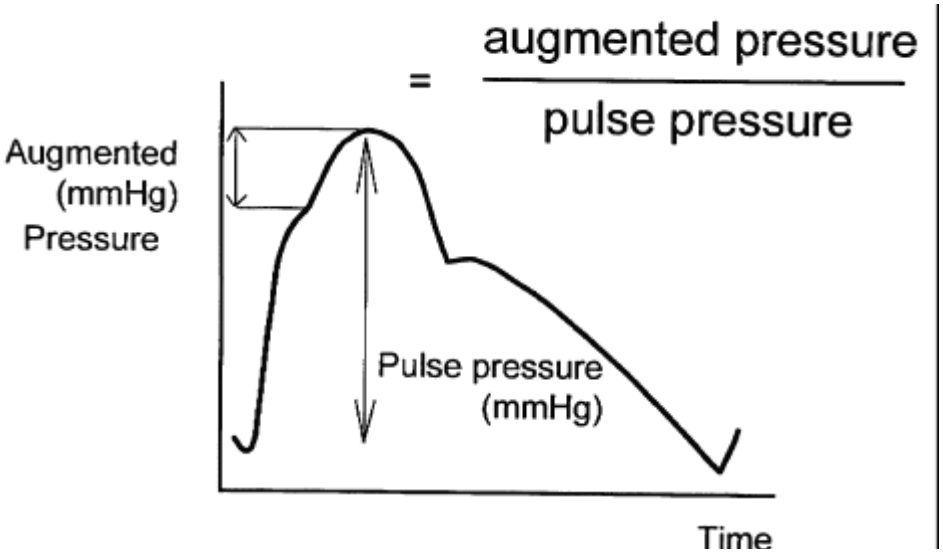


Figure 4. Calculation of the augmentation index (%). (109)

Autonomic dysfunction also leads to an increase in the likelihood of hypertension (115). In women with FM who have autonomic dysfunction, higher levels of resting BP have been reported (94, 95). However, these data are not universal (38). Studies utilizing women with FM have also reported that the responses of BP to a physiological stressor, such as orthostasis, are altered compared to HC (94).

Acute endurance exercise has been shown to decrease aortic wave reflection (102) and BP in young men and women (37, 63, 83-85). However, less is known about the effects of acute resistance exercise on aortic wave reflection and BP (24, 82, 108). Lydakis et al. (81) reported that isometric handgrip at 40% maximal voluntary contraction until fatigue decreased the compliance of the central arteries in young men and women such that there was an increased AIa (70%) and a reduction in the transit time of the reflected wave (Tr)(5.7%). MacDonald et al. (86) reported a significant decrease of 20 mmHg in central systolic BP (SBP) from 30-60 minutes of recovery from an acute resistance exercise bout in young women. Meanwhile, O'Conner et al. (108) have suggested that an acute bout of resistance exercise does not alter BP in young women.

Our pilot data (71) demonstrate a significant increase in SBP and diastolic BP (DBP) in women with FM and HC groups of women during IHG (Figures 5 & 6). However, there was a group-by-time interaction for SBP, such that women with FM had a lower increase in SBP than

HC. Our data suggest an impaired sympathetic control in women with FM that may contribute to the lower increase in SBP by decreasing myocardial contractility and stroke volume.

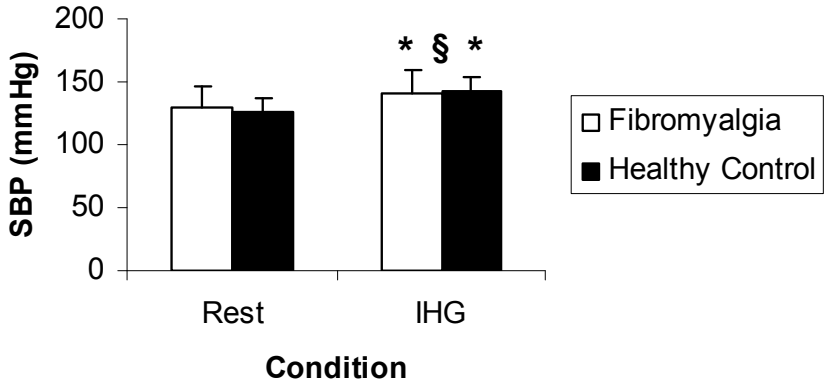


Figure 5. Differences in SBP in women with FM (n=11) compared to HC (n=9) at rest and during IHG. There is a group-by-time interaction (§ $p<0.05$) due to a larger increase in the HC and a main effect of condition for both groups ($p<0.05$) (* different from Rest). Values are mean ± SD. (71)

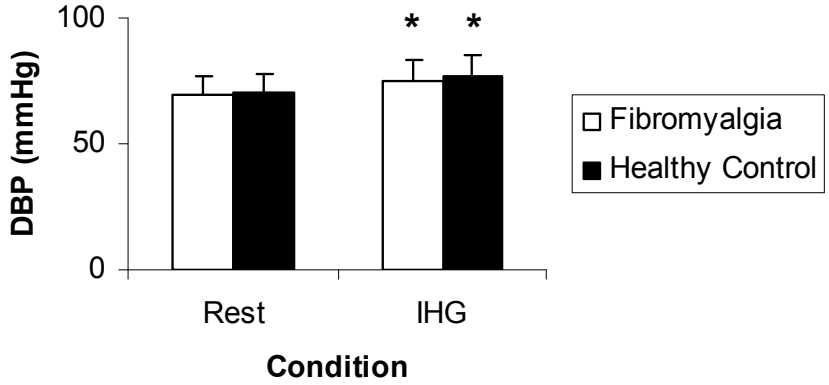


Figure 6. Differences in DBP in women with FM (n=11) compared to HC (n=9) at rest and during IHG. There is a main effect of time for both groups ($p<0.05$) (* different from Rest). Values are mean ± SD. (71)

The effects of RET on aortic wave reflection (11, 13, 25, 53) and BP (10, 12, 69) are mixed. Cortez-Cooper et al. (25) demonstrated that 11 weeks of high-intensity RET alters aortic wave reflection at rest in young women. On the other hand, Casey et al. published no significant

changes of aortic wave reflection in young women (11) or postmenopausal women (13) following RET. Carter and colleagues (10) reported that high-intensity RET decreased BP measurements in young men and women. On the contrary, Olson et al. (113) and Casey et al. (13) demonstrated that RET had no effect on BP in premenopausal or postmenopausal women, respectively.

Forearm Blood Flow and Vasodilatory Capacity

Venous occlusion strain-gauge plethysmography (VOP) is a noninvasive method for evaluation of flow-mediated dilation (FMD). VOP utilizes a mercury-filled strain gauge to assess changes in blood flow (4, 55, 57). VOP quantifies changes in FBF induced by reactive hyperemia (RH), which is due to endothelium-dependent dilation (4, 55). The measurement derived from VOP is based on the increase in blood volume after occlusion of venous return by a pneumatic cuff. It is known that FMD in response to RH is endothelium dependent. Responses to RH are attenuated in those with hypertension, diabetes mellitus, dyslipidemia, heart failure and smokers (55, 57).

While increases in FBF and vasodilatory capacity have been reported to occur after acute aerobic exercise the data are limited concerning acute resistance exercise. Baynard et al. (4) demonstrated that aerobically-trained men have a greater capacity for vasodilation compared to resistance-trained men at rest. In a study by DeVan and colleagues (28), an acute bout of resistance exercise utilizing 9 exercises at 75% of the pre-determined 1-RM decreased carotid artery compliance for 30 minutes after exercise cessation. A recent study by Fahs et al.(32), who utilized 4 sets of 5 repetitions on the bench press at 80% of the 1-RM followed by 4 sets of 10 repetitions at 70% of the 1-RM on the biceps curl, reported an increase in FBF of roughly 70% and an increase in the blood flow responses to RH by 65%.

Increases in FBF and vasodilatory capacity have been found to occur after endurance training (4, 16, 56, 73). The increases in both FBF and vasodilatory capacity in response to RH have been attributed to repeated bouts of vascular sheer stress that in turn increases levels of nitric oxide (NO), a potent vasodilator (4, 56). While studies have demonstrated increases in FBF with isometric handgrip training (3) and circuit training (16), the responses to full-body resistance exercise training (RET) are mixed (11, 25, 101, 123). Casey et al. (11) demonstrated that 18 weeks of RET in postmenopausal women did not alter resting FBF. On the contrary,

Rakabowchuk et al. (123) reported that 12 weeks of RET increased FBF and vasodilatory capacity but did not change flow-mediated dilation in healthy men and women.

While there appears to be evidence suggesting reduced vascular perfusion in women with FM, it is not conclusive (31, 80, 98). Researchers have reported that women with FM have structural abnormalities, including reduced capillary bed volume as well as dysfunction of the capillary endothelium (31, 98). Lund et al. (80) reported reduced tissue oxygenation in the trapezius and brachioradialis in women with FM compared to healthy controls. Reduced blood flow to the supraspinatus has been reported by Elvin and others (31) after static and dynamic exercise, but not at rest. The data published by Elvin et al. (31) suggest that modifications of blood flow are altered in response to an acute exercise stressor in women with FM.

Summary

Fibromyalgia is an idiopathic rheumatoid disease characterized by pain upon pressure of 11 out of 18 tender points across the body and a multitude of symptoms (146). These symptoms can include: orthostatic intolerance, irritable bowel, parasthesis, cold allodynia, fatigue, and reduced muscular strength. The etiology of FM is not well understood and it is more prevalent in women (90%) than men. Recent research has suggested that many of the characteristics of FM may be explained by dysfunctions of the autonomic nervous system (20, 94, 122) and the endothelium (114). Sympathetic hyperactivity (93) and vascular dysfunction, result in reduced blood flow that may be involved in symptoms of FM such as pain (136) and exercise intolerance (68). Changes in blood flow induced by RH measured through VOP may yield valuable insight into endothelium-dependent vasodilation (52, 62, 105). The AIa is a noninvasive measurement of arterial wave reflection (25, 105). Previous evidence suggests that resistance exercise may be effective in reducing some of the symptoms of FM including the number of active tender points (116, 142), myalgic score (91, 116) and the FIQ (116, 129), as well as the reduction in muscular strength and endurance (72). However, the effects of resistance exercise on autonomic modulation and vascular function have not been investigated in women with FM.

CHAPTER 3: METHODS

Participants. Participants were recruited from the local community through newspaper advertisements. Of the initial 332 women that were interviewed, only 29 women between 35-50 years participated in the study (Figure 7). Participants were categorized as either being clinically diagnosed with FM (n=9) or as healthy controls (HC) (n=20). Inclusion criteria included diagnosis of FM by a board-certified rheumatologist (146), age between 35 and 50 years, premenopausal and no history of chronic diseases. Women were excluded if they had exercised within the past year, smoked within the past 6 months, had hypothyroidism, history of cancer, any pituitary disease, vascular disease, severe depression, hypertension (≥160/100 mmHg), coronary artery disease, pregnant or contemplating pregnancy, diabetes, a BMI under 25 kg/m^2 or over 35 kg/m^2, taking any form of estrogen/progesterone, or taking any medications that altered cardiovascular function. Medications that were being taken by the women with FM included sleep aids (n=3) and painkillers (n=1). None of the HC were taking any medication. All participants gave written consent as approved by the Institutional Review Board of the Florida State University (Appendix A).

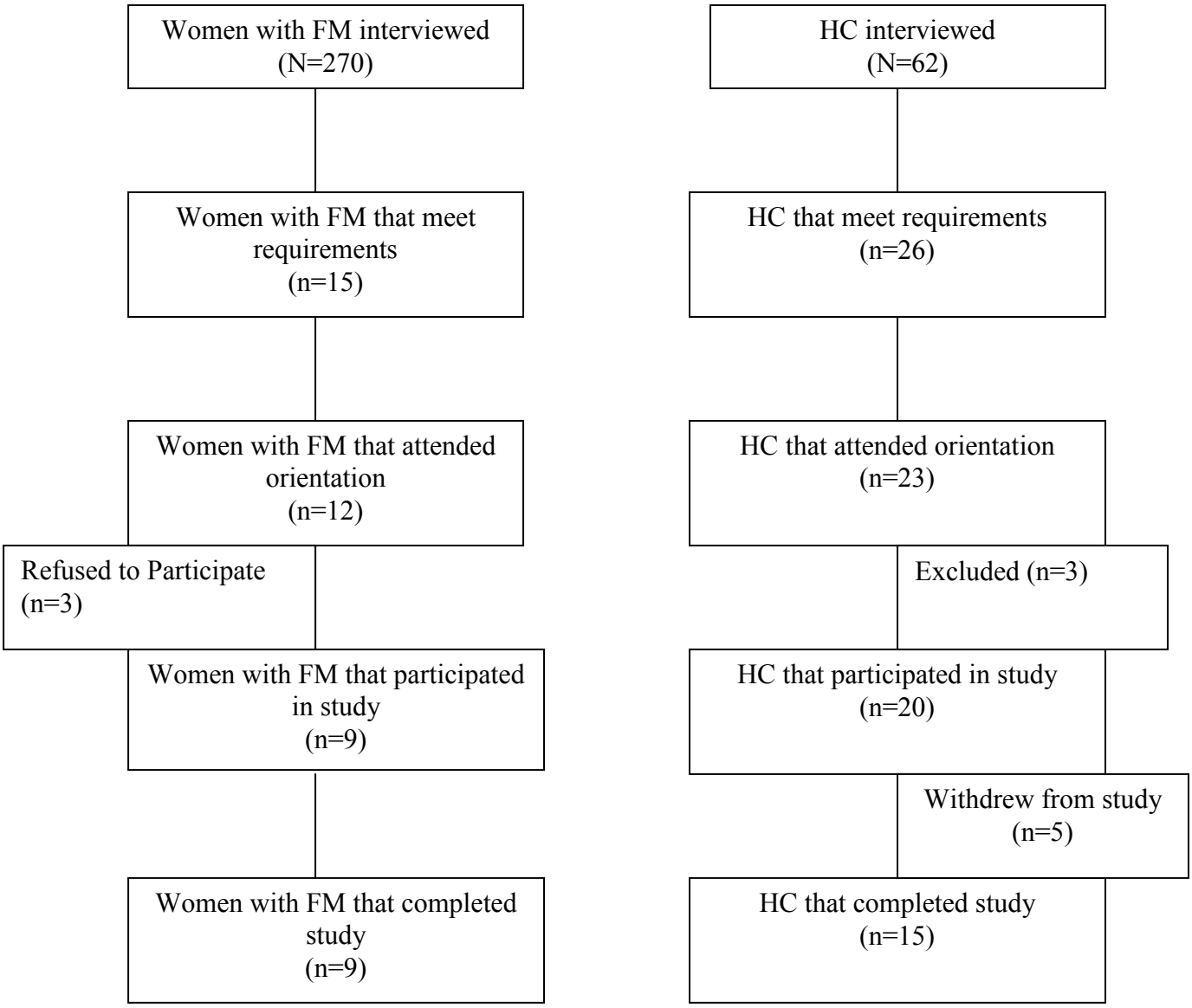


Figure 7. Flow diagram of progress of participants through the study.

Study Design. Participants were tested at baseline (Pre1), after a 4-week control period (Pre2), and after a 12-week RET period (Post) (Figure 8). Testing at each time period occurred over 2 weeks. The initial visit consisted of an orientation, which included signing of the informed consent, questionnaires on health history (Appendix C) and demographics were completed and the participants received physician consent forms. The number of active tender points (Appendix G), myalgic score and the FIQ (Appendix D) were collected on the second visit during the visit to the Rheumatology clinic. Participants then underwent measurements of muscle strength and anthropometrics on both the third and fourth visits (Appendix H). The fifth visit consisted of measurements of autonomic modulation, aortic wave reflection and blood pressures in response to a CPT before and after acute resistance exercise (Appendix E). One week following this test, the sixth or seventh visit, participants returned to the laboratory to undergo measurements of FBF and vasodilatory capacity before and after an acute bout of resistance exercise (Appendix F). All measurements at the three time periods were conducted at the same time of day to reduce possible diurnal physiological variations. Participants were asked to maintain their current habits over the course of the study.

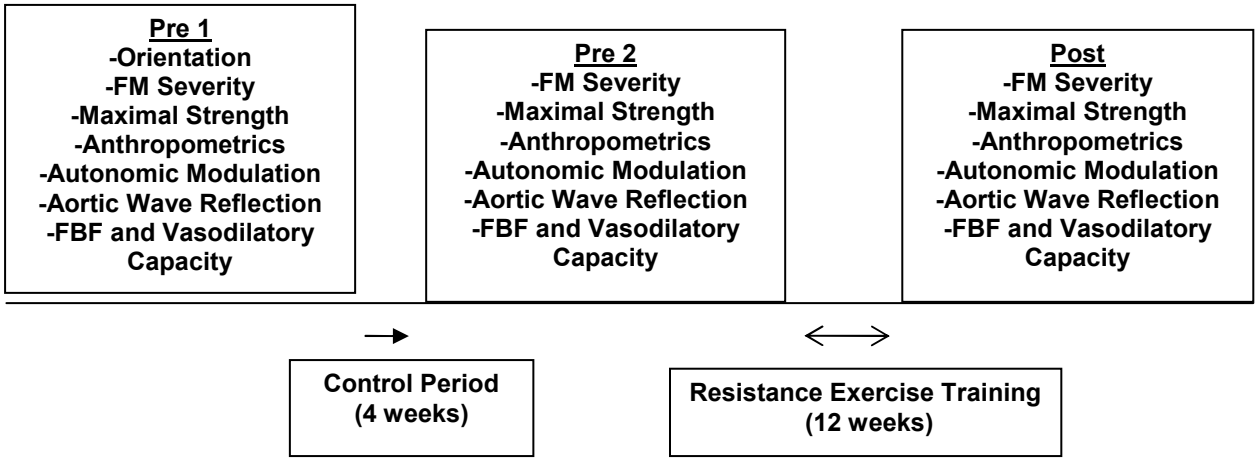


Figure 8. Timetable for data collection.

Health History Questionnaire. A health history questionnaire was given to each participant at the beginning of the study. The questionnaire included questions pertaining to medication usage,

any previous and/or current diagnoses, and any pain felt during menstruation (using a 10-point numerical scale) (Appendix C).

Tender Points. All women underwent diagnosis of FM by a board certified rheumatologist in a blinded manner to confirm diagnosis of FM according to the guidelines of American College of Rheumatology (V. McMillan) (Figure 1) (146) at all time periods (Appendix G). The women were examined for both the number of active tender points and total myalgic score. The total myalgic score was assessed by assigning each active tender point a sensitivity score of 0 (no pain) to 3 (withdrawal of the subject from the examiner) for each of the 18 tender points, which were totaled for a possible total myalgic score of 54 units (58). A total of 11 out of 18 specific tender points was required for eligibility in the FM group (Figure 8). The rheumatologist was blinded to the group assignments of the participants, but not to the intervention.

Fibromyalgia Impact Questionnaire. The FIQ was utilized to determine the impact of FM on a week-to-week basis (9). The FIQ consists of 20 questions that assess items such as the ability to perform activities of daily living, well-being, and symptoms of FM. The greater the FIQ score, the greater the impact of the disease (Appendix D). Researchers have demonstrated that the average woman with FM scores 50 units, while a more severely impacted woman with FM has scores of 70 units and above (90). The FIQ has been shown to be both a reliable and valid questionnaire for impact of FM (9).

Anthropometry. Body weight was measured on a Seca (Hanover, MD) balance beam scale to the nearest 0.1 lb, which was subsequently converted to kilograms for further analysis. Height was measured with a Medart stadiometer (St. Louis, MI) to the nearest cm. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Maximal Strength. Maximal strength was performed using the 1-RM test for the chest press, leg press, seated row, leg extension, and leg curl on MedX^{TM} machines (Appendix H). After a brief warm-up with a light resistance load, participants were progressed until a resistance load was ascertained that could be moved one time through a complete range of motion. All measurements were recorded within 3-5 attempts. Following a minimum of 72 hours of rest,

participants returned for verification of the 1-RM. The highest resistance load attained was defined as the 1-RM.

Acute Effects of Resistance Exercise on Aortic Wave Reflection, Autonomic Function and Blood Pressure. Participants arrived at the laboratory following a 12-hour fast, no caffeine ingestion for at least 12 hours and having abstained from strenuous exercise for 24 hours. After 10-minutes of rest in the seated position, brachial BP was assessed using an automated, non-invasive blood pressure cuff (Omron). Three measurements were taken on the non-dominant arm, with at least one minute between each measure. The average of the three measurements was used as the resting measurement. All other BP measurements were collected by the method described below. Following another 10-minute rest period, autonomic modulation, resting digital and aortic SBP, DBP, PP, and mean arterial pressure (MAP), AIa, AIa@75, and Tr were collected during 5 minutes (Figure 9). Thereafter, the 2-minute CPT1 was administered. The aortic wave reflection was determined with 30 seconds remaining in each CPT while BP was continuously recorded. Immediately after exercise cessation, the participants returned to the seated position. Post-exercise electrocardiogram (ECG), aortic wave reflection and BP were collected between minutes 20 to 25 followed by a 2-minute CPT. A metronome was set so that we could regulate the participant's breathing at 12 breaths/minute during all collection of ECG data.

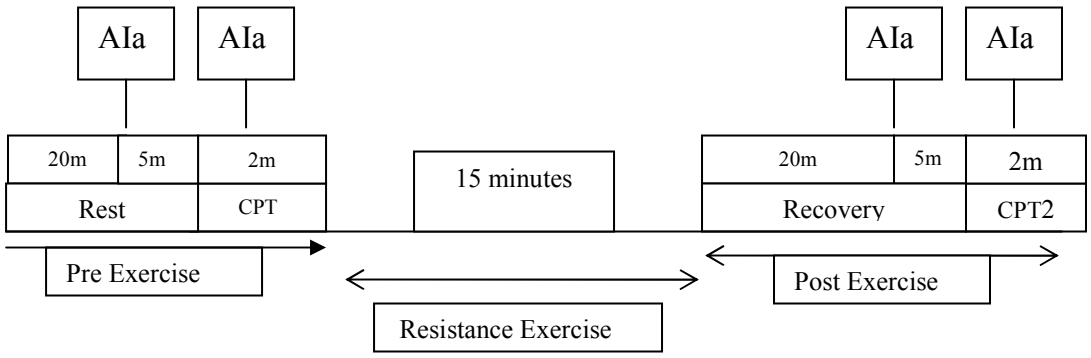


Figure 9. Timeline for testing the effects of acute resistance exercise and the cold pressor test (CPT) on autonomic modulation, aortic wave reflection and BP.

Heart Rate Variability. Heart rate variability was evaluated in the manner described by the European Task Force on HRV (2). ECG signals were collected at a rate of 1000Hz using a

modified CM5 configuration. The WinCPRS (Absolute Aliens Oy, Turku, Finland) software was used to import ECG and to extract the beat-by-beat R to R interval (RRI) following visual inspection of noise, ectopics and artifacts. Since small sections of beats were collected, 2-5 minutes, Fast Fourier Transformation was used to generate spectral power and time domains. Total power of HRV is used as an index of total autonomic nervous system activity. Studies suggest that LF (0.04-0.15 Hz) power of HRV is mediated by both sympathetic and parasympathetic modulations (2, 79, 118). High-frequency (0.15 -0.4 Hz) power of HRV is indicative of parasympathetic modulation (2). The power for each individual frequency is evaluated by examination of the total area under the curve for that component and may be expressed in absolute (ms^2) or normalized (nu) units (2). Normalization is assessed by dividing the power of a component (HF or LF) by the total power, and then multiplying by 100 (2). In the present study power spectral densities were calculated in absolute units as well as nu for LF (LFnu) and HF (HFnu). HFnu demonstrates vagal modulation while LFnu, along with the LF/HF ratio, are indicative of sympathetic modulation and sympathovagal balance (2, 18, 20). In the time domain, overall assessment of autonomic modulation was quantified using SDNN (2). Vagal modulation was determined by RMSSD and the pNN50 index (2).

Aortic Wave Reflection. The aortic wave reflection characteristics were evaluated using the SphygmoCor system (AtCor Medical, Sydney, Australia). The radial pulse waveform was recorded through radial applanation tonometry. The aortic pressure waveform was derived from the radial applanation tonometry using a generalized transfer function implemented within the SphygmoCor software. The generalized transfer function has been shown to be both reliable and valid (111). The augmentation of the aortic SBP (AIa; Figure 4) was calculated as the differences between the first and second systolic peak divided by the pulse pressure (PP) and multiplied by 100. Since the AIa is influenced by HR, it was normalized to 75 bpm (AIa@75). The Tr from the ascending aorta to the reflection site and back is measured from the foot of the forward traveling pressure wave to the foot of the reflected wave. Radial artery waveforms were calibrated using the Finometer.

Blood Pressure. Blood pressure was measured continuously throughout all data collection using finger photoplethysmography (Finometer). The finger was kept at the hydrostatic indifference

point at all times during testing. Before data collection, measurements were confirmed with resting brachial BP values collected by an automated sphygmomanometer (Omron).

Cold Pressor Test. To evaluate responses to sympathetic mediated increases in HR, aortic wave reflection and BP the CPT was administered at rest (CPT1) and during recovery from acute resistance exercise (CPT2). The CPT was performed by immersion of the right hand up to the wrist in cold water (10°C) for 2 minutes. The water was circulated by a technician throughout the entire test in order to prevent heat build-up around the hand (100).

Acute Resistance Exercise. The acute resistance exercise was administered consisting of 5 sets of 10-RM on the leg press (MedX ^{TM}). The ten repetition maximum (10-RM) was derived from the previously determined 1-RM using the equation from Brzycki (8). A 2-minute rest period was given between each set. When subjects were fatigued, assistance was given on the last 1-3 repetitions so that the required 10 repetitions could be completed with proper form. The acute resistance exercise bout lasted 15 minutes.

Acute Resistance Exercise on Forearm Blood Flow and Vasodilatory Capacity. FBF and vasodilatory capacity were measured in the supine position after a 20-minute rest period and 15-minutes after the acute resistance exercise protocol using strain-gauge plethysmography (EC-6, D.E. Hokanson Inc., Bellevue, WA) one week after the CPT (Figure 10). A mercury-filled strain gauge was placed around the widest part of the forearm to measure changes in forearm volume. A cuff was placed around the upper arm and the wrist. The wrist cuff was inflated to 100 mmHg one minute prior to measurement of FBF to occlude hand circulation. The upper arm cuff was inflated to 40 mmHg for 8 seconds followed by a 7-second deflation for each 15-second cycle to determine resting FBF (55). FBF were calculated using an average of 6 plethysmographic cycles and expressed as ml/min/100 ml of blood (55). Following collection of FBF, peak vasodilatory capacity was measured using RH. An upper arm cuff was inflated to 240 mmHg for 4 minutes to occlude forearm circulation. The wrist cuff was inflated to 50 mmHg 1 minute prior release of the upper arm cuff. Fifteen seconds after the upper arm cuff was deflated, changes in forearm volume were recorded for 3 minutes (55). Data are presented as alterations in forearm blood flow volume over time (vasodilatory capacity) and as responses of blood flow to RH. The

responses to RH were plotted into a curve, and the area under the curve (AUC) was used as a measure of RH blood flow.

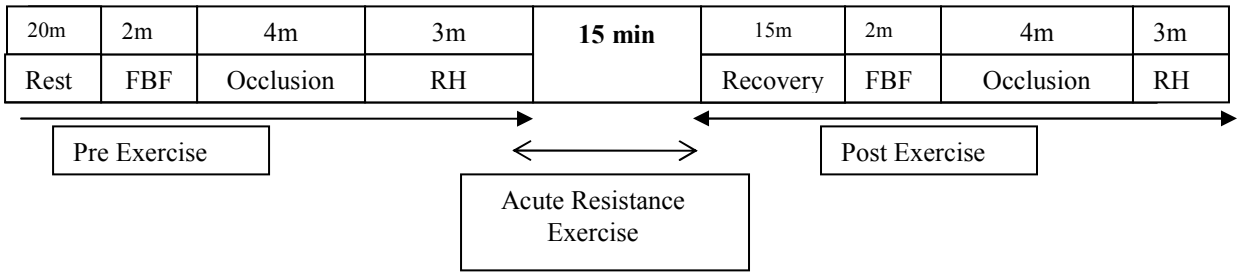


Figure 10. Timeline for testing effects of acute resistance exercise on forearm blood flow and vasodilatory capacity.

Resistance exercise training. Supervised RET was performed twice a week, with each session separated by at least 48 hours. The training protocol included the MedX chest press, leg extension, leg press, seated row, and leg curl exercises. Participants began RET with 3 sets of each exercise at 50-60% of the 1-RM for upper and lower body, respectively. When the participant was able to perform 3 sets of 12 repetitions on 2 consecutive training days, the resistance was increased by 2-10% as recommended by the American College of Sports Medicine (1). Training sessions lasted approximately 30 minutes.

Statistics. Effect size was calculated using the formula:

$$\text{Effect size} = \frac{\text{(Mean Pre Test – Mean Post Test)}}{\text{Standard Deviation of Pre/Post (largest)}}$$

Alpha was set at 0.05 and power at 80%. Izdebska (59) reported decreases in LF_{SAP} ($14.9\pm1.8 mmHg^2$ to $16.8\pm1.2 mmHg^2$) in healthy young women after endurance training for 12 weeks. From this an effect size of 1.05 and 8 volunteers would be needed. Based on data by Olson (113) in overweight, premenopausal women reported an increase in FBF from 6.3±3.49% to 8.9±3.49% before and after resistance training, respectively. The effect size is 0.74 and estimates 15 volunteers per group.

The baseline characteristics of the groups were analyzed using Student's t-test. Since a Kolmogorov-Smirnov normality test determined that absolute values for total power, LF and HF were not normally distributed, they were subsequently transformed to their natural logarithm (Ln). A repeated measures analysis of variance (ANOVA) was used to test the effects of group (FM vs. HC) and time (Pre1, Pre2 and Post) on the number of active tender points, myalgic score, the FIQ and maximal strength. A second ANOVA was used to determine the effects of group across time and condition (rest, CPT1, recovery, and CPT2) on HR, LF, HF, LF/HF ratio, LFnu, HFnu, LFnu/HFnu ratio, RRI, SDNN, RMSSD, pNN50 Index, AIa, AIa@75, Tr, digital SBP, DBP, PP, MAP and aortic SBP, DBP, PP, MAP. Multivariate ANOVAs with repeated measures on the last factor were used to determine group differences across time (Pre1, Pre2, Post) and condition (pre-exercise vs. post-exercise) on FBF, vasodilatory capacity and RH blood flow. When main effects were demonstrated, t-tests were used for post-hoc comparisons. When examining vasodilatory capacity over time, a Bonferroni's adjustment was made. Significance was set *a priori* at $p<0.05$. Values are presented as mean ± SD. All statistical analyses were performed using SPSS Version 17 (SPSS, Inc., Chicago, IL, USA).

CHAPTER 4: RESULTS

Five of the 20 original HC withdrew from the study prior to RET due to family-related issues (n=3) or scheduling conflicts (n=2). No women with FM withdrew from the study. In addition, one HC participant fainted during each of her CPT trials. We were able to collect 90 seconds of HRV and BP but were unable to obtain aortic wave reflection in this participant during the CPTs. Therefore, 15 HC are included in the analyses for maximal strength, FM severity, autonomic modulation and digital and aortic BP, FBF and vasodilatory capacity, while only 14 HC are included in the analyses of aortic wave reflection. All women with FM were able to complete each CPT. Adherence to the RET was similar between groups (FM vs. HC: 88 vs. 91%, $p>0.05$). There were no group differences in age, height, weight, and BMI, or pain felt during the menstrual cycle (using a 10-point numerical scale)(Appendix) (Table 1) at any time point between the women with FM and the HC. Participant characteristics did not change over time.

Table 1. Participant Characteristics at Pre1, Pre2 and Post for Women with FM (n=9) and HC (n=15).

Variable	Pre1	Pre2	Post
Disease Duration, years			
FM	7±3	-	-
HC	-	-	-
Pain During Menstruation, units			
FM	5±3	-	-
HC	3±2	-	-
Age, yrs			
FM	42±5	-	-
HC	45±5	-	-
Height, m			
FM	1.64±0.06	-	-
HC	1.67±0.07	-	-
Weight, kg			
FM	80.2±9.1	80.8±9.8	81.4±9.6
HC	77.6±10.1	77.2±9.7	76.6±9.1

Table 1 – continued

Variable	Pre1	Pre2	Post
Body Mass Index, kg/m^2			
FM	30.2±3.6	30.4±3.4	30.4±3.2
HC	27.5±2.4	27.4±2.3	27.2±1.8

Values are mean ± SD
FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

Maximal Strength and FM Severity

The number of active tender points, myalgic score and FIQ were significantly (p<0.05) greater in women with FM than the HC at all time periods. In the women with FM, RET reduced the number of active tender points (Pre1: 13±2, Pre2: 13±2, Post: 8±4 units; p<0.05), the myalgic score (Pre1: 14±2, Pre2:13±3, Post: 8±4 units; p<0.05), and FIQ (Pre1: 57±17, Pre2: 52±17, Post: 42±16 units; p<0.05) (Table 2). There was no difference in maximal strength at Pre1, Pre2 or Post between women with FM and HC (Table 3). Maximal strength increased significantly (p<0.05) in response to RET in both groups for the chest press (FM vs. HC: 24.0 vs. 24.6%), leg press (25.0 vs. 20.8%), seated row (18.6 vs. 16.4%), leg extension (28.3 vs. 27.4%) and leg curl (22.0 vs. 27.7%). Participants finished training at 83% of their 1-RM for the chest press, 91% for the leg press, 71% on the seated row, 79% on the leg extension and 87% on the leg curl.

Table 2. Number of Active Tender Points, Myalgic Score and the Fibromyalgia Impact Questionnaire at Pre1, Pre2 and Post in Women with FM (n=9) and HC (n=15).

Variable	Pre1	Pre2	Post
Tender Points, units			
FM	13±2 Ψ	13±3 Ψ	8±4 Ψ ‡
HC	0	0	0
Myalgic Score, units			
FM	14±2 Ψ	13±3 Ψ	8±4 Ψ ‡
HC	0	0	0

Table 2 – continued

Variable	Pre1	Pre2	Post
FIQ, units			
FM	56.8±16.7 Ψ	52.0±17.5 Ψ	41.6±15.5 Ψ ‡
HC	8.2±7.0	7.7±7.5	8.0±7.9

Values are mean ± SD
‡p<0.05, significantly different from Pre1 and Pre2
Ψ p<0.05, significantly different from HC
FM=Women with Fibromyalgia; HC=Healthy Controls; FIQ=Fibromyalgia Impact Questionnaire; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

Table 3. Maximal Strength in Women with FM (n=9) and Healthy Controls (n=15) at Pre1, Pre2 and Post.

Variable	Pre1	Pre2	Post
Chest Press, AU			
FM	217±25	219±32	288±41 ‡
HC	197±50	199±51	264±48 ‡
Leg Press, AU			
FM	308±59	326±58	440±62 ‡
HC	331±54	338±58	427±60 ‡
Seated Row, AU			
FM	227±38	232±38	285±50 ‡
HC	219±40.2	225±36	269±43 ‡
Leg Extension, AU			
FM	237±30	238±26	332±52‡
HC	245±42	244±43	336±43 ‡
Leg Curl, AU			
FM	194±29	195±28	250±26 ‡
HC	178±23	183±29	253±27 ‡

Values are mean ± SD
‡ p<0.05, significantly different from Pre1 and Pre2
FM=Women with Fibromyalgia; HC=Healthy Controls; AU=arbitrary units; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

Autonomic Modulation

Pre-exercise and Post-exercise Responses Before and After RET. There was no group by time by condition interaction for HR and HRV during CPT1 and CPT2 before and after RET (Table 4). HR increased significantly (p<0.05) at Pre1 and Post, but not at Pre2. Ln LF significantly increased (p<0.05) in response to CPT1 only at Pre2 and it approached significance Post (p=0.07); there was no effect at Pre1. There was a significant (p<0.05) increase of LFnu at CPT1 for Pre2 and Post. LFnu increased during CPT1 at Pre1 but it was not significant (p=0.08), it was significant (p<0.05) at Pre2 and Post (Figure 11). HFnu decreased significantly (p<0.05) during CPT1 at Pre2 and Post and was also reduced during Pre1 (p=0.08) (Figure 12). HR increased compared to rest in response to CPT2 at Pre1 (p=0.06) and increased significantly (p<0.05) at Pre2 and Post. Although not different across time, there was a significant (p<0.05) increase in HR from recovery to CPT2 after RET. Ln LF was increased significantly (p<0.05) above rest at Pre2 and Post during recovery and further increased during CPT2 at only Pre2 such that it was elevated above rest and recovery. The Ln LF/Ln HF ratio was elevated above rest during recovery (p<0.05) and elevated above recovery during CPT2 (p<0.05) at Pre1. The Ln LF/Ln HF ratio was significantly (p<0.05) elevated above rest during CPT1 at Pre2 and approached significance (p=0.08) at Post. The Ln LF/Ln HF ratio was also elevated above rest (p<0.05) during CPT2 at Pre2 and Post. During recovery, normalized indices of HRV were altered compared to rest, but they were not significant (p=0.06). There was a reduced magnitude of change for LFnu and HFnu from recovery to CPT2 such that they were statistically different from rest during CPT2, but were not different from recovery. The LFnu/HFnu ratio was elevated above rest (p<0.05) during CPT2 at all time periods. At Pre2, the LFnu/HFnu ratio was elevated above rest (p<0.05) during CPT1 and the responses to CPT2 were attenuated compared to CPT1 (p<0.05). There was no effect of time or condition on any time domain of HRV.

Table 4. Heart Rate and Heart Rate Variability during Rest, CPT1, Recovery and CPT2 at Pre1, Pre2 and Post in Women with FM (n=9) and HC (n=15).

Pre1

Variable	Rest	CPT1	Recovery	CPT2
Heart Rate, bpm				
FM	82±11	84±9*	79±9	84±10 γ
HC	72±7	76±9*	76±9	80±14 γ

Table 4 – continued

Variable	Rest	CPT1	Recovery	CPT2
Ln Total Power, ms^2				
FM	6.6±0.9	6.9±0.5	6.6±0.7	6.5±0.7
HC	7.1±0.8	7.1±0.9	7.2±1.7	7.0±1.1
Ln Low Frequency, ms^2				
FM	4.7±0.6	5.1±0.8	5.1±1.0	5.2±0.7
HC	5.6±1.2	5.7±1.1	5.5±1.6	5.8±1.8
Ln High Frequency, ms^2				
FM	5.7±0.8	5.6±0.9	5.5±1.4	5.4±0.9
HC	6.1±1.1	6.2±1.4	6.0±1.7	6.0±2.5
Ln LF/Ln HF ratio				
FM	0.44±0.27	0.64±0.35	0.90±0.74*	1.03±0.83*†
HC	0.83±5.6	1.42±1.66	0.89±0.80*	1.10±0.74*†
Normalized Low-Frequency, %				
FM	28.1±12.0	36.2±11.6 γ	40.1±19.6	44.2±16.7*
HC	39.4±17.0	46.9±20.1 γ	39.9±16.5	48.2±21.7*
Normalized High-Frequency, %				
FM	70.9±11.9	62.2±11.6 γ	58.1±18.9	54.3±16.2*
HC	58.3±18.3	51.4±19.5 γ	58.1±16.6	49.7±21.0*
LFnu/HFnu ratio				
FM	0.83±0.10	0.90±0.09	1.20±0.36	0.94±0.17*
HC	0.93±0.14	0.92±0.14	1.06±0.27	0.940.13*
RRI, ms				
FM	794±116	785±98	791±105	780±96
HC	863±99	866±109	810±129	826±128
SDNN, units				
FM	33.9±7.1	39±4.2	37.7±20.1	32.0±14.4
HC	50.9±25.2	55.3±30.8	42.8±24.0	43.4±20.5
RMSSD, units				
FM	22.8±4.8	23.7±7.6	29.7±29.8	23±14.8
HC	34.1±22.1	30.1±13.4	30.2±22.2	29.7±19.9
pNN50 Index				
FM	2.4±2.8	4.2±4.1	8.6±13.8	5.3±10.1
HC	9.2±15.1	14.4±19.2	6.4±9.8	8.6±13.0

Table 4 – continued

Values are mean ± SD
*p<0.05, significantly different from rest
†p<0.05, significantly different from recovery
γ p=0.08, different from rest
Ln=Natural Log Transformation; CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET; LF=Low-Frequency; HF=High Frequency; RRI= R-to-R Interval; SDNN=Standard Deviation of the Normal RR intervals; RMSSD=Root Mean Squared Difference of Successive RR Intervals; pNN50 Index=Proportion of Interval Differences of Successive RR intervals Greater than 50 ms.

Pre2

Variable	Rest	CPT1	Recovery	CPT2
Heart Rate, bpm				
FM	81±8	85±10	80±9	82±11*
HC	75±15	81±2	78±19	81±17*
Ln Total Power, ms^2				
FM	6.2±0.6	6.6±0.9	6.6±0.8	7.0±0.7
HC	6.8±0.7	7.0±0.9	7.0±0.9	6.9±0.8
Ln Low Frequency, ms^2				
FM	4.3±0.9	5.0±1.6*	5.0±1.1*	5.3±1.0*†
HC	5.2±0.4	5.6±1.1*	5.5±1.5*	5.9±1.7*†
Ln High Frequency, ms^2				
FM	4.9±0.6	4.5±1.1	5.1±1.1	5.3±0.9
HC	5.7±1.0	5.4±1.3	5.9±1.7	6.1±2.4
Ln LF/Ln HF Ratio				
FM	0.72±0.44	3.01±2.88*	1.53±1.42	1.34±0.93*
HC	0.86±0.76	2.66±3.1*	0.90±0.63	1.36±1.18*
Normalized Low-Frequency, %				
FM	37.8±16.1	61.3±25.7*	50.0±22.5γ	49.7±20.3*
HC	39.3±18.4	54.2±26.2*	42.3±13.9 γ	47.9±21.0*
Normalized High-Frequency, %				
FM	60.8±16.1	37.4±25.9*	48.5±22.4 γ	49.1±20.4*
HC	58.7±18.0	44.5±26.0*	56.2±14.3 γ	50.0±20.6*

Table 4 – continued

Variable	Rest	CPT1	Recovery	CPT2
LFnu/HFnu Ratio				
FM	0.89±0.17	1.17±0.50*	0.93±0.16	1.03±0.25*#
HC	0.93±0.15	1.13±0.40*	0.99±0.15	0.96±0.11*#
RRI, ms				
FM	780±87	785±70	801±92	772±72
HC	861±196	883±188	834±203	855±186
SDNN, units				
FM	26.3±7.4	37.8±13.1	33.4±12.3	36.8±14.5
HC	40.5±21.3	43.7±22.1	38.9±13.1	43.1±17.3
RMSSD, units				
FM	15.9±3.8	15.9±5.3	21.2±15.7	19.1±7.0
HC	31.5±24.3	28.3±13.2	26.7±15.6	28.5±15.5
pNN50 Index				
FM	0.73±1.2	1.3±1.9	2.5±4.0	1.7±2.7
HC	9.5±16.0	8.2±7.1	4.3±4.3	7.7±9.1

Values are mean ± SD
*p<0.05, significantly different from rest
†p<0.05, significantly different from recovery
#p<0.05, significantly different from CPT1
γp=0.06, different from rest
Ln=Natural Log Transformation; CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.; LF=Low-Frequency; HF=High Frequency; RRI= R-to-R Interval; SDNN=Standard Deviation of the Normal RR intervals; RMSSD=Root Mean Squared Difference of Successive RR Intervals; pNN50 Index=Proportion of Interval Differences of Successive RR intervals Greater than 50 ms.

Post

Variable	Rest	CPT1	Recovery	CPT2
Heart Rate, bpm				
FM	78±9	83±10*	79±14	84±13*†
HC	75±12	80±14*	76±11	81±14*†

Table 4 – continued

Variable	Rest	CPT1	Recovery	CPT2
Ln Total Power, ms^2				
FM	6.6±1.2	6.5±0.6	6.8±0.9	6.8±0.9
HC	6.8±0.9	7.2±1.0	7.0±0.7	7.0±0.7
Ln Low Frequency, ms^2				
FM	4.9±1.0	5.0±1.0	5.2±1.0	5.5±0.8*
HC	5.2±1.1	5.8±1.0	5.5±0.7	5.7±0.9*
Ln High Frequency, ms^2				
FM	5.3±1.0	5.2±1.1	5.3±0.9	5.2±1.0
HC	5.7±0.8	5.9±1.1	5.6±1.0	5.6±1.0
Ln LF/Ln HF Ratio				
FM	0.94±0.82	1.14±0.89γ	1.24±0.86	1.89±1.74*
HC	1.00±1.10	1.24±0.97γ	1.75±3.03	1.89±2.08*
Normalized Low-Frequency, %				
FM	40.9±18.6	46.0±18.7*	47.3±21.4 γ	55.2±20.1*
HC	38.8±21.6	48.1±18.7*	46.3±20.6γ	50.5±20.4*
Normalized High-Frequency, %				
FM	57.3±18.4	52.7±18.8*	50.5±20.9 γ	44.7±21.1*
HC	58.1±21.2	49.8±17.7*	51.4±19.4 γ	46.8±21.7*
LFnu/HFnu Ratio				
FM	0.94±0.15	0.98±0.15	0.98±0.20	0.99±0.19*
HC	0.92±0.19	0.99±0.14	0.98±0.20	1.01±0.22*
RRI, ms				
FM	745±68	799±162	795±138	755±82
HC	877±171	895±162	849±171	841±138
SDNN, units				
FM	31.5±15.5	34.5±18.2	34.7±14.7	31.4±16.4
HC	39.5±15.5	49.4±21.3	42.2±16.9	46.2±16.7
RMSSD, units				
FM	20.2±9.9	18.3±9.9	23.8±13.5	23.1±16.6
HC	31.1±15.7	32.7±16.4	29.1±16.8	31.7±19.6
pNN50 Index				
FM	4.4±6.4	3.7±7.6	4.5±6.9	3.7±6.8
HC	9.5±11.4	11.1±13.5	9.4±11.8	8.6±12.3

Table 4 - continued

Values are mean ± SD
*p<0.05, significantly different from rest
†*p*<0.05, significantly different from recovery
γ*p*=0.06, different from rest
Ln=Natural Log Transformation; CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET; LF=Low-Frequency; HF=High Frequency; RRI= R-to-R Interval; SDNN=Standard Deviation of the Normal RR intervals; RMSSD=Root Mean Squared Difference of Successive RR Intervals; pNN50 Index=Proportion of Interval Differences of Successive RR intervals Greater than 50 ms.

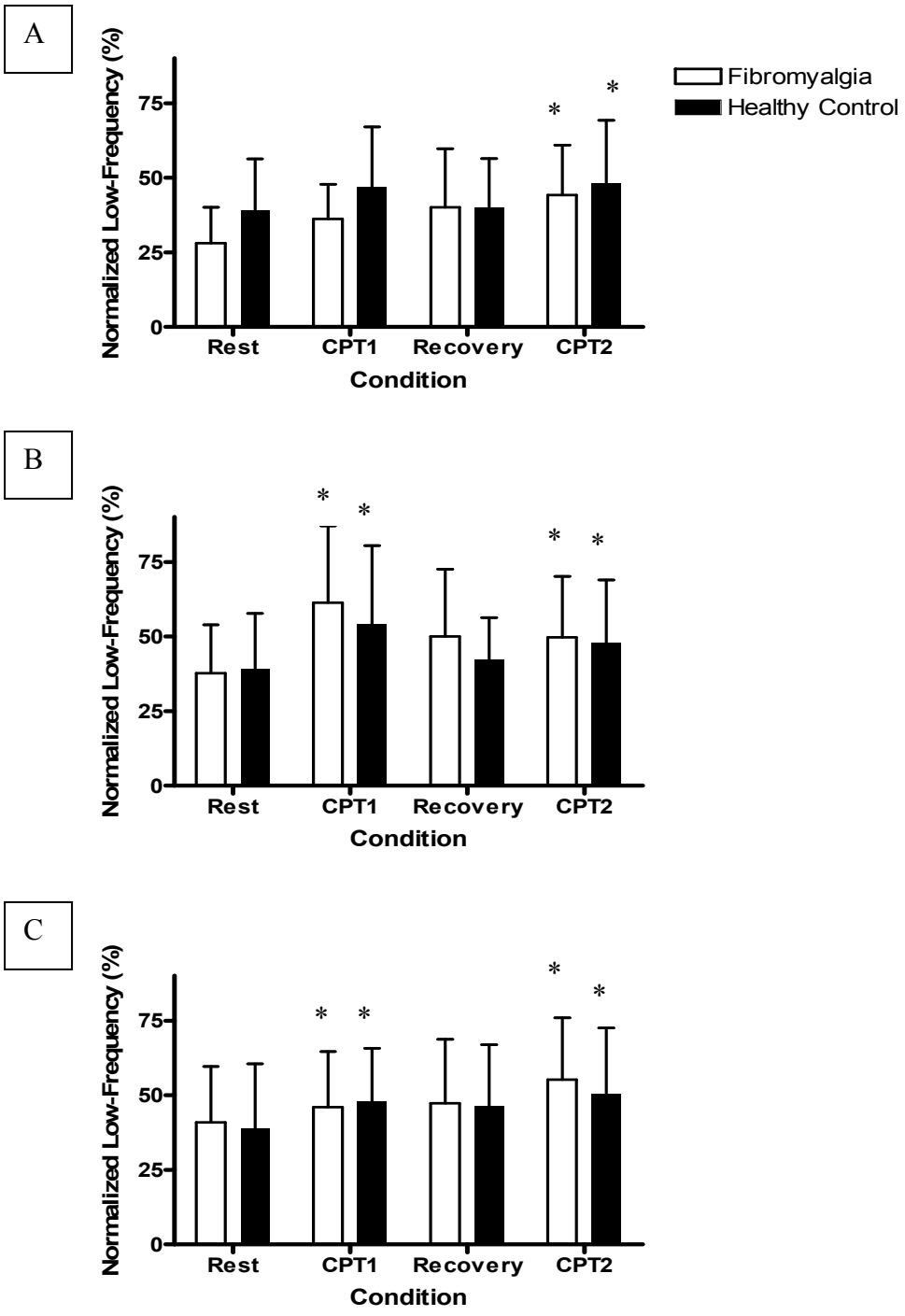


Figure 11. Normalized low-frequency power at rest, CPT1, recovery and CPT2 at A) Pre1, B) Pre2 and C) Post in women with FM (n=9) and HC (n=15). *p<0.05, significantly different from rest. Values are mean ± SD. CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test.

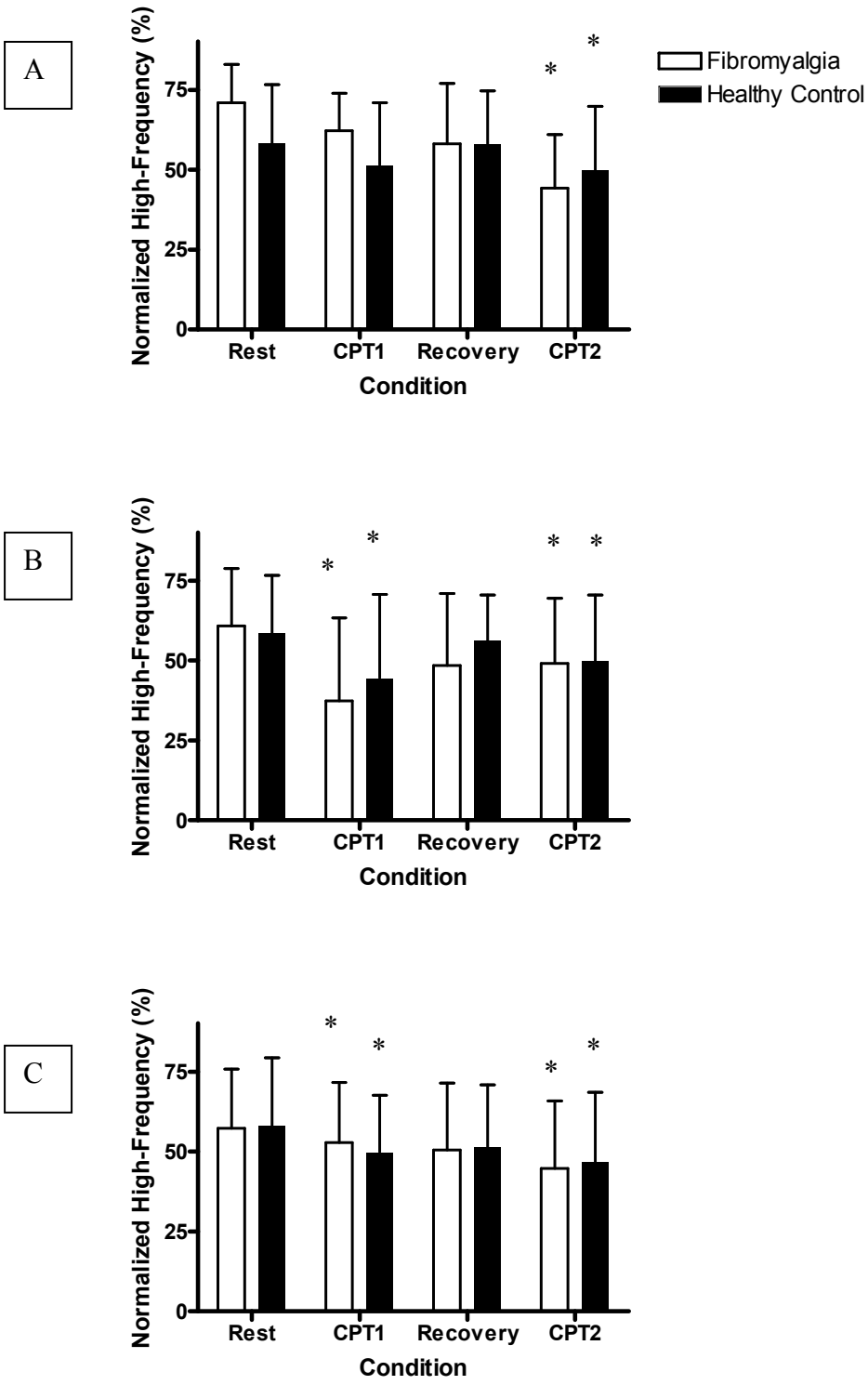


Figure 12. Normalized high-frequency power at rest, CPT1, recovery and CPT2 at A) Pre1, B) Pre2 and C) Post in women with FM (n=9) and HC (n=15). * $p<0.05$, significantly different from rest. Values are mean ± SD. CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test.

Aortic Wave Reflection and Blood Pressure

Pre-exercise and Post-exercise Responses of Aortic Wave Reflection Before and After RET. Measurements for aortic wave reflection are presented in Table 5 while BP measurements are presented in Table 6. There was no group x condition interaction for aortic wave reflection at rest or during CPT1 at any time period. The AIa increased significantly (p<0.05) in response to the CPT1 at Pre2 and Post but not at Pre1. There was also a condition effect for the AIa@75 such that it increased significantly during CPT1 at Pre1 (p<0.05) and Pre2 (p<0.05) and approached significance Post (p=0.07). There was no effect of CPT1 on Tr in either group.

There was a main effect of the acute resistance exercise such that AIa was decreased during recovery compared to rest at Pre1 (p<0.05) but not Pre2 and Post. The AIa was elevated by CPT2 compared to recovery at Pre1 (p<0.05) and compared to recovery and rest at Pre2 (p<0.05). The magnitude of change for AIa in response to CPT2 at Post was significantly (p<0.05) attenuated compared to CPT1. The AIa@75 increased significantly (p<0.05) above recovery and rest in response to CPT2 at Pre1 and Pre2 but not Post. At Post the response of AIa@75 to CPT2 was reduced compared to the response during CPT1. Tr was significantly reduced in response to CPT2 compared to recovery at Pre1 (p<0.05) and Pre2 (p<0.05), but the magnitude of change was not significant Post (p=0.07).

Table 5. Measurements of Aortic Wave Reflection during Rest, CPT1, CPT2 and Recovery for of at Pre1, Pre2 and Post in Women with FM (n=9) and HC (n=14).

Pre1

Variable	Rest	CPT1	Recovery	CPT2
AIa, %				
FM	28.9±9.5	30.7±8.1	25.8±9.0*	29.9±8.8†
HC	28.5±6.6	29.8±7.9	24.9±8.9*	27.7±11.0†
AIa@75, %				
FM	29.8±10.5	31.9±9.0*	28.4±7.1	31.3±7.6*†
HC	27.1±6.4	28.4±6.9*	26.4±4.7	28.8±5.3*†
Tr, ms				
FM	133.9±12.3	132.1±11.9	137.6±10.8	130.4±7.2†
HC	138.1±12.5	132.6±10.2	138.5±8.1	133.2±10.4†

Values are mean ± SD

Table 5 – continued

*p<0.05, significantly different from rest
†p<0.05, significantly different from recovery
CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test; AIa=Aortic Augmentation Index; AIa@75=Aortic Augmentation Index normalized at 75 bpm; Tr=Reflection Time; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

Pre2

Variable		Rest	CPT1	Recovery	CPT2
AIa, %					
	FM	26.6±9.0	31.4±9.9*	27.6±10.2	30.5±7.2*†
	HC	28.1±10.1	31.0±10.1*	24.7±11.1	28.4±11.3*†
AIa@75, %					
	FM	27.9±9.7	32.2±9.8*	29.5±6.8	32.0±7.4*†
	HC	27.7±5.5	29.4±6.4*	25.4±7.5	28.0±7.4*†
Tr, ms					
	FM	137.3±12.1	133.5±13.7	135.9±10.8	132.8±5.2†
	HC	135.5±9.6	133.4±8.0	139.4±11.7	135.5±13.4†

Values are mean ± SD
*p<0.05, significantly different from rest
†p<0.05, significantly different from recovery
CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test;; AIa=Aortic Augmentation Index; AIa@75=Aortic Augmentation Index normalized at 75 bpm; Tr=Reflection Time; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

Post

Variable		Rest	CPT1	Recovery	CPT2
AIa, %					
	FM	26.0±8.4	29.6±6.4*	27.5±8.9	27.2±9.6#
	HC	29.9±6.5	32.3±10.9*	26.5±9.4	28.6±11.3#
AIa@75, %					
	FM	27.9±5.9	29.7±6.5¥	28.0±10.3	28.4±10.8
	HC	28.2±5.6	31.2±5.8¥	26.7±4.3	28.9±6.1

Table 5 – continued

Variable	Rest	CPT1	Recovery	CPT2
Tr, ms				
FM	137.2±6.2	134.8±9.6	140.1±17.7	139.5±18.0γ
HC	138.4±9.8	132.6±8.3	138.4±10.0	137.4±8.6γ

Values are mean ± SD
*p<0.05, significantly different from rest
†p<0.05, significantly different from recovery
#p<0.05, significantly different from CPT1
¥p=0.07, different from rest
γp=0.07, different from recovery
CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test; AIa=Aortic Augmentation Index; AIa@75=Aortic Augmentation Index normalized at 75 bpm; Tr=Reflection Time; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

Pre-exercise and Post-exercise Responses of Blood Pressure before and after RET. There was no group x time x condition effect for peripheral or central BP. The digital SBP and the aortic SBP were unaffected by RET or CPT1 in either group (Table 5 and Figure 13). Digital DBP decreased due to CPT1 in both groups at Pre1 (p<0.05), Pre2 (p<0.05) and decreased significantly only for the HC at Post (p<0.05); it approached significance for women with FM (p=0.08). Aortic DBP decreased significantly (p<0.05) in response to the CPT1 at all times (Figure 14). Digital PP and aortic PP significantly (p<0.05) increased for each group at Pre1, Pre2, and Post in response to CPT1 (Figure 15). Digital mean arterial pressure (MAP) and aortic MAP both decreased significantly (p<0.05) in response to CPT1 at all time periods (Figure 16).

Digital SBP was not altered by the acute resistance exercise or by CPT2 at any time period. Additionally, aortic SBP was reduced during recovery compared to rest at Pre1 (p<0.05). Digital DBP and aortic DBP were significantly (p<0.05) decreased by the CPT1, acute resistance exercise, and CPT2 compared to rest. Digital and aortic PP were elevated above resting levels significantly (p<0.05) during recovery, but only digital and aortic PP were increased during CPT2. Digital and aortic MAP were decreased compared to rest during recovery at all time periods. During CPT2, aortic MAP was reduced compared to rest while digital MAP returned to resting values. Even though not significant across time, after RET the responses of aortic DBP, digital and aortic MAP to CPT2 were reduced compared to the responses elicited by CPT1.

Table 6. Peripheral and Estimated Aortic Blood Pressure during Rest, CPT1, CPT2 and Recovery at Pre1, Pre2 and Post in Women with FM (n=9) and HC (n=14).

Pre1

Variable	Rest	CPT1	Recovery	CPT2
Digital blood pressure				
Systolic blood pressure, mmHg				
FM	122±16	123±23	116±11	123±26
HC	116±10	119±10	109±13	112±13
Diastolic blood pressure, mmHg				
FM	86±11	76±11*	68±5*	75±15*
HC	79±6	69±8*	65±9*	66±9*
Pulse pressure, mmHg				
FM	36±9	48±14*	48±9*	48±17*
HC	38±9	51±11*	44±9*	46±11*
Mean arterial pressure, mmHg				
FM	102±15	93±15*	85±7*	95±13
HC	94±8	85±7*	79±9*	80±12
Estimated aortic blood pressure				
Aortic systolic blood pressure, mmHg				
FM	116±17	115±22	107±12*	114±22α#
HC	109±8	110±10	97±13*	103±12α#
Aortic diastolic blood pressure, mmHg				
FM	88±11	72±11*	69±6*	76±16*
HC	80±6	70±8*	66±9*	68±9*
Aortic pulse pressure, mmHg				
FM	28±9	36±10*	38±8*	37±14*
HC	30±7	41±10*	34±8*	36±9*
Aortic mean arterial pressure, mmHg				
FM	97±13	89±5*	83±7*	93±12*
HC	89±6	83±8*	83±7*	78±11*

Values are mean ± SD
*p<0.05, significantly different from rest
#p<0.05, significantly different from pre-exercise CPT (CPT1)
α p=0.06, different from recovery

Table 6 – continued

CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

	Pre2			
Variable	Rest	CPT1	Recovery	CPT2
Digital blood pressure				
Systolic blood pressure, mmHg				
FM	114±9	115±14	118±13	113±17
HC	114±11	112±13	116±14	117±17
Diastolic blood pressure, mmHg				
FM	80±5	68±7*	70±8*	65±19*
HC	78±7	65±10*	69±7*	65±10*
Pulse pressure, mmHg				
FM	34±6	47±10*	47±7*	47±7*
HC	36±7	48±14*	47±10*	48±10*
Mean arterial pressure, mmHg				
FM	91±6	86±7*	87±10*	85±6
HC	91±6	80±9*	85±10*	83±15
Estimated aortic blood pressure				
Aortic systolic blood pressure, mmHg				
FM	107±8	107±12	109±14	104±14#
HC	107±10	103±10	106±13	108±17#
Aortic diastolic blood pressure, mmHg				
FM	81±5	70±7*	72±8*	67±10*
HC	79±7	67±9*	71±7*	71±11*
Aortic pulse pressure, mmHg				
FM	26±4	37±8*	38±7*	37±7*
HC	28±6	38±11*	35±10*	37±10*
Aortic mean arterial pressure, mmHg				
FM	89±6	84±7*	85±11*	83±5*
HC	89±8	78±9*	82±9*	81±14*

Values are mean ± SD
*$p<0.05$, significantly different from rest

Table 6 – continued

#$p<0.05$, significantly different from CPT1
CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

Table 6 – continued

		Post		
Variable	Rest	CPT1	Recovery	CPT2
Digital blood pressure				
Systolic blood pressure, mmHg				
FM	113±7	123±8	118±8	120±12
HC	120±10	120±15	117±18	113±18
Diastolic blood pressure, mmHg				
FM	79±9	75±6Ψ	70±6*	71±4*
HC	82±8	72±10*	69±8*	67±10*
Pulse pressure, mmHg				
FM	35±7	48±9*	48±5*	49±11*
HC	36±5	48±10*	46±12*	46±11*
Mean arterial pressure, mmHg				
FM	91±7	91±5*	86±6*	87±6#
HC	94±8	88±11*	84±10*	83±6#
Estimated aortic blood pressure				
Aortic systolic blood pressure, mmHg				
FM	106±7	113±7	108±9	110±11#
HC	113±10	112±16	107±18	104±17#
Aortic diastolic blood pressure, mmHg				
FM	80±8	76±6*	72±6*	73±4*#
HC	83±8	74±10*	70±8*	69±10*#
Aortic pulse pressure, mmHg				
FM	26±4	37±7*	36±6*	37±9*
HC	28±4	38±10*	35±11*	36±10*
Aortic mean arterial pressure, mmHg				
FM	89±8	89±5*	84±7*	85±5*#
HC	92±8	86±11*	82±10*	81±12*#

Values are mean ± SD

Table 6 – continued

*p<0.05, significantly different from rest
#p<0.05, significantly different from pre-exercise CPT (CPT1)
Ψp=0.08, different from rest
CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test; FM=Women with Fibromyalgia; HC=Healthy Controls; Pre1=Baseline; Pre2=After 4-week control period; Post=After 12 weeks of RET.

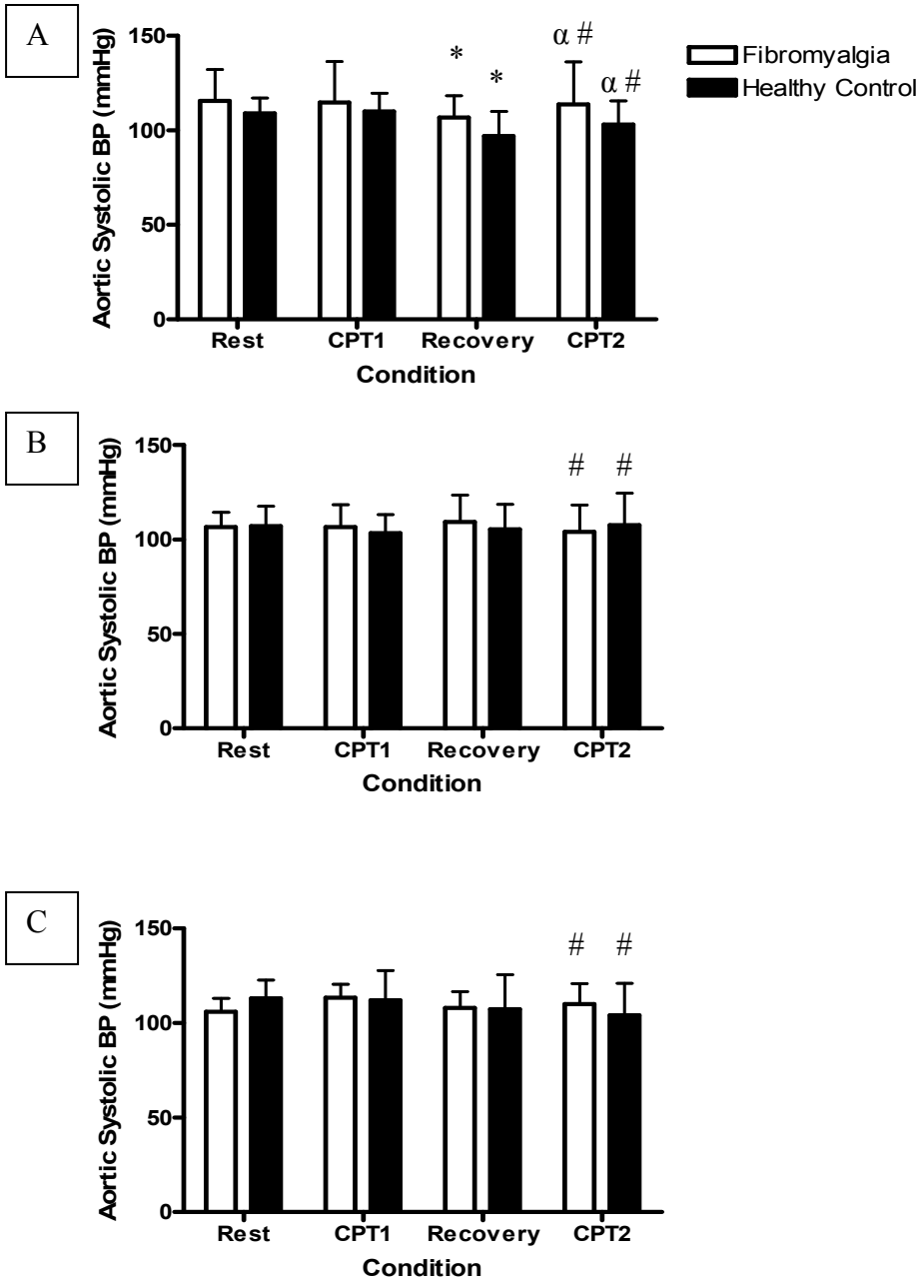


Figure 13. Aortic systolic BP at rest, CPT1, recovery and CPT2 at A) Pre1, B) Pre2 and C) Post in women with FM (n=9) and HC (n=15). * $p<0.05$, significantly different from rest, #$p<0.05$, significantly different from (CPT1),α $p=0.06$, different from recovery. Values are mean ± SD. CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test.

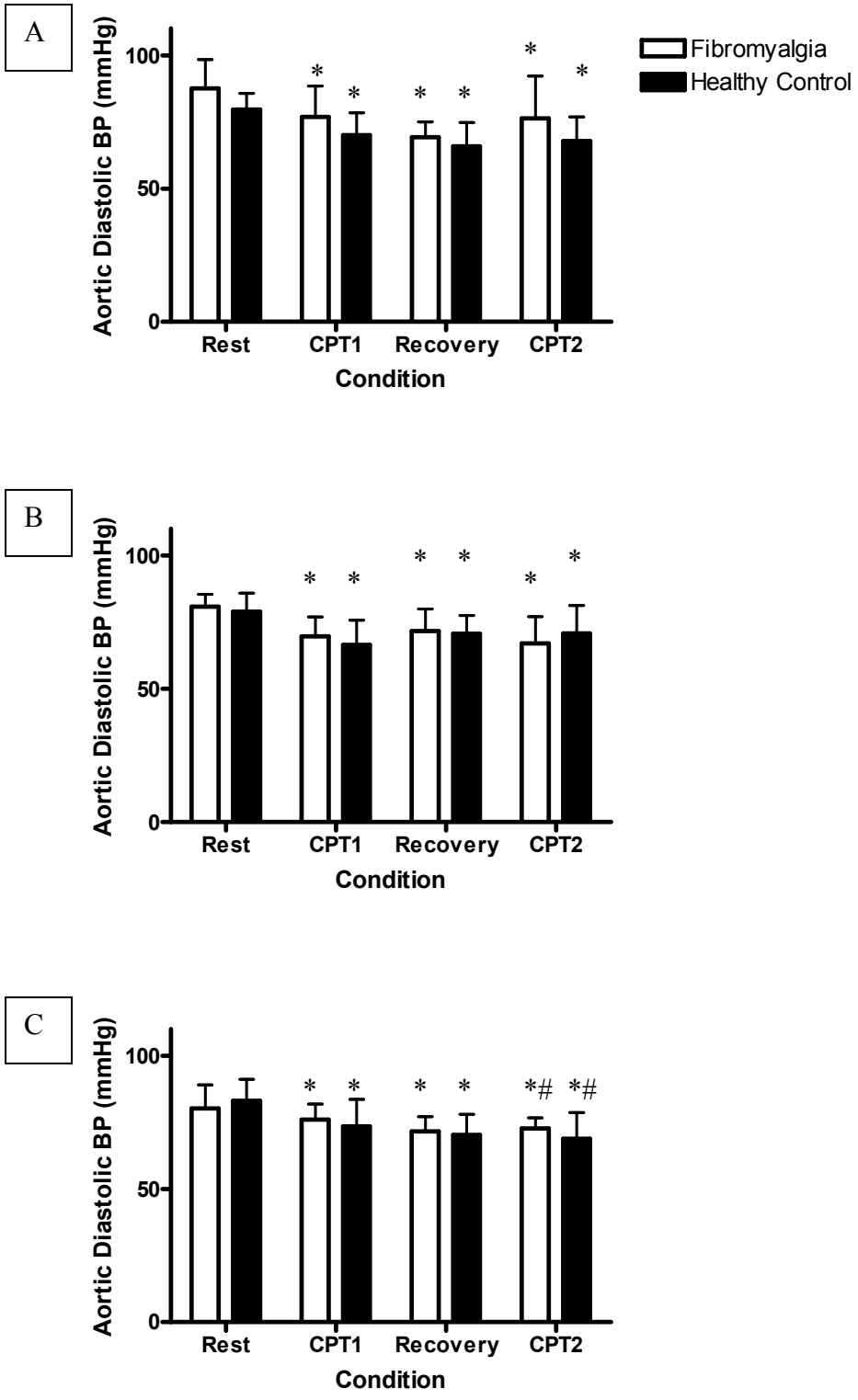


Figure 14. Aortic diastolic BP at rest, CPT1, recovery and CPT2 at A) Pre1, B) Pre2 and C) Post in women with FM (n=9) and HC (n=15). * $p<0.05$, significantly different from rest, #$p<0.05$, significantly different from CPT1. Values are mean ± SD. CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test.

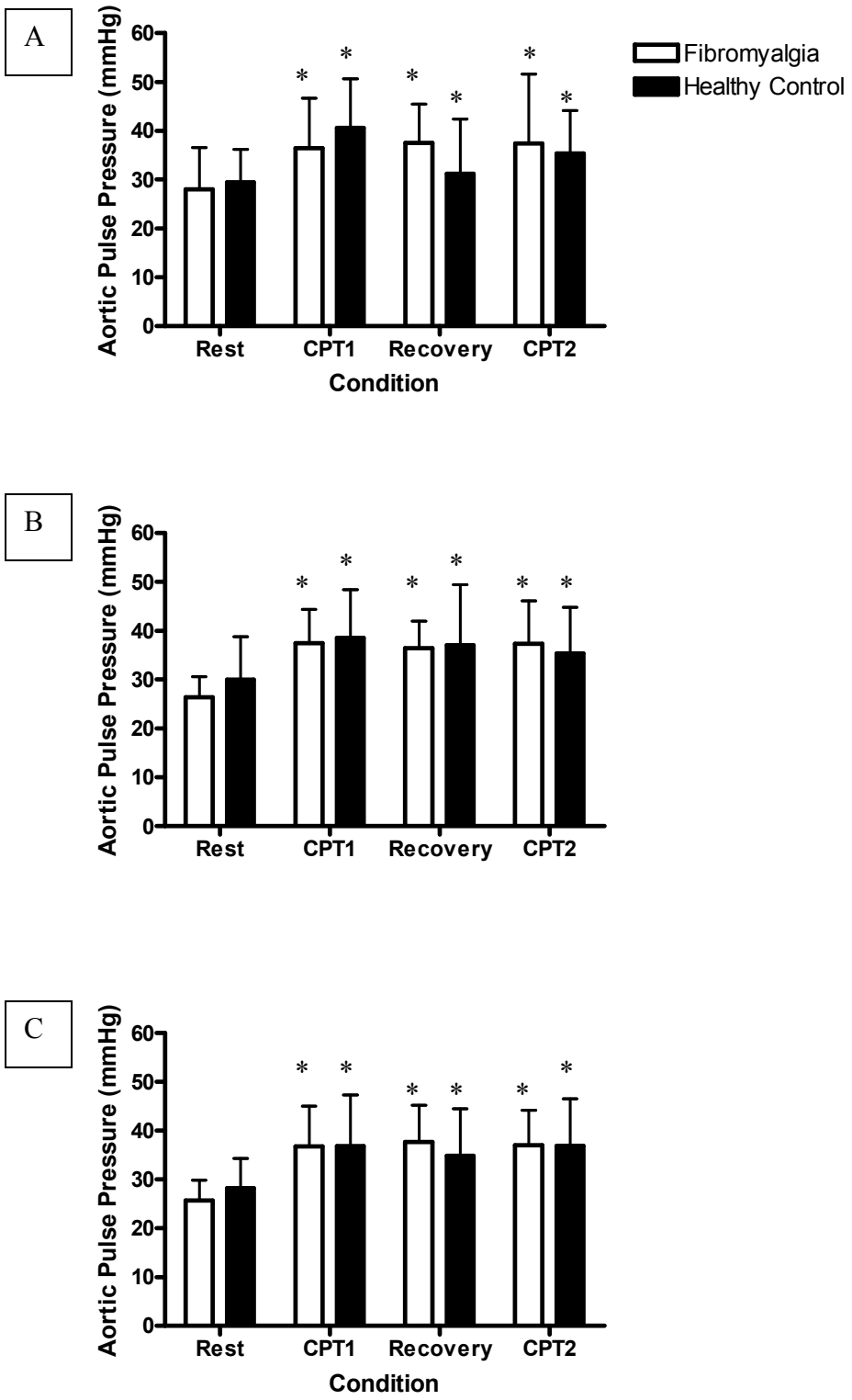


Figure 15. Aortic pulse pressure at rest, CPT1, recovery and CPT2 at A) Pre1, B) Pre2 and C) Post in women with FM (n=9) and HC (n=15). * $p<0.05$, significantly different from rest. Values are mean ± SD. CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test.

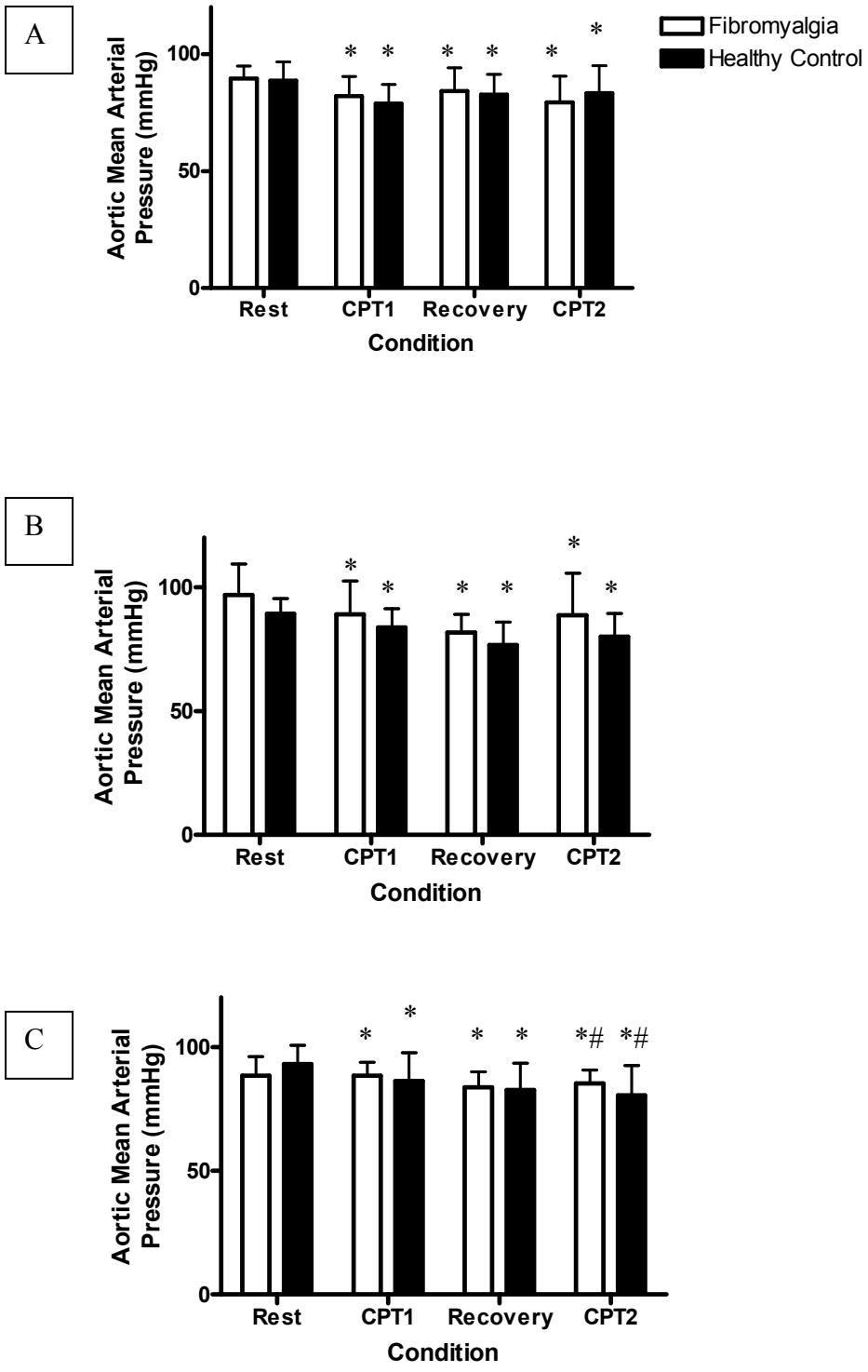


Figure 16. Aortic mean arterial pressure at rest, CPT1, recovery and CPT2 at A) Pre1, B) Pre2 and C) Post in women with FM (n=9) and HC (n=15). * $p<0.05$, significantly different from rest, #$p<0.05$, significantly different from CPT1. Values are mean ± SD. CPT1=Pre-exercise cold pressor test; CPT2=Post-exercise cold pressor test.

FBF and Vasodilatory Responses

Pre-exercise and Post-exercise Responses before RET. There was no group by time interactions for FBF, vasodilatory capacity or blood flow responses to RH. Vasodilatory capacity was significantly (p<0.05) increased above pre-exercise FBF for both groups at Pre1 and Pre2. Recovery FBF was not altered by the acute resistance exercise compared to rest. The post-exercise vasodilatory capacity was significantly (p<0.05) elevated above the post-exercise FBF at Pre1 (FM vs. HC: 221.1 vs. 205.5%) and Pre2 (135.2 vs. 213.9%). There was no effect of the acute resistance exercise on RH blood flow at Pre1 or Pre2 (Figure 19).

Pre-exercise Responses after RET. There were no group by time interactions for pre-exercise FBF or vasodilatory capacity. Pre-exercise FBF significantly (p<0.05) increased after RET compared to Pre1 and Pre2 in women with FM (50.6% and 48.8%) and HC (43% and 30.3%)(Figure 13). Pre-exercise vasodilatory capacity was significantly (p<0.05) increased compared to pre-exercise FBF (FM vs. HC: 124.4 vs. 195.7%). Pre-exercise vasodilatory capacity also increased significantly at Post in women with FM (p<0.05) and HC (p<0.05) compared to Pre1 (38.5% vs. 15.2%) and Pre2 (45.9% vs. 28.0%) (Figure 17). Pre-exercise RH blood flow was also significantly elevated compared to Pre1 (FM vs. HC: 47.0% vs. 23.7%, p<0.05) and Pre2 (FM vs. HC: 37.3% vs. 31.2%, p<0.05).

Post-exercise Responses after RET. The workload increased significantly (p<0.05) after RET in women with FM (29.9%) and in the healthy controls (22.5%) compared to Pre1 (Table 2). There was no group by time interaction for post-exercise FBF and vasodilatory capacity before and after RET (Figures 17 and 18). Post-exercise FBF significantly increased (p<0.05) after RET compared to Pre1 and Pre2 in women with FM (49.4% and 49.1%) and HC (43.6% and 30.3%). Post-exercise vasodilatory capacity increased significantly (p<0.05) compared to post-exercise FBF at Pre1 (FM vs. HC: 221.1 vs. 205.5%) and Pre2 (135.2 vs. 213.9%) and Post (134.1 vs. 202%). The post-exercise vasodilatory capacity increased in both groups in response to RET compared to Pre1 (FM vs. HC: 38.7 vs. 28.6%, p<0.05) and Pre 2 (FM vs. HC: 36.2 vs. 23.6%, p<0.05). RH blood flow after acute resistance exercise was significantly (p<0.05) elevated in both groups in response to RET compared to Pre1 (FM vs. HC: 45.9% vs. 31.5%) and Pre2 (38.5% vs. 18.8%).

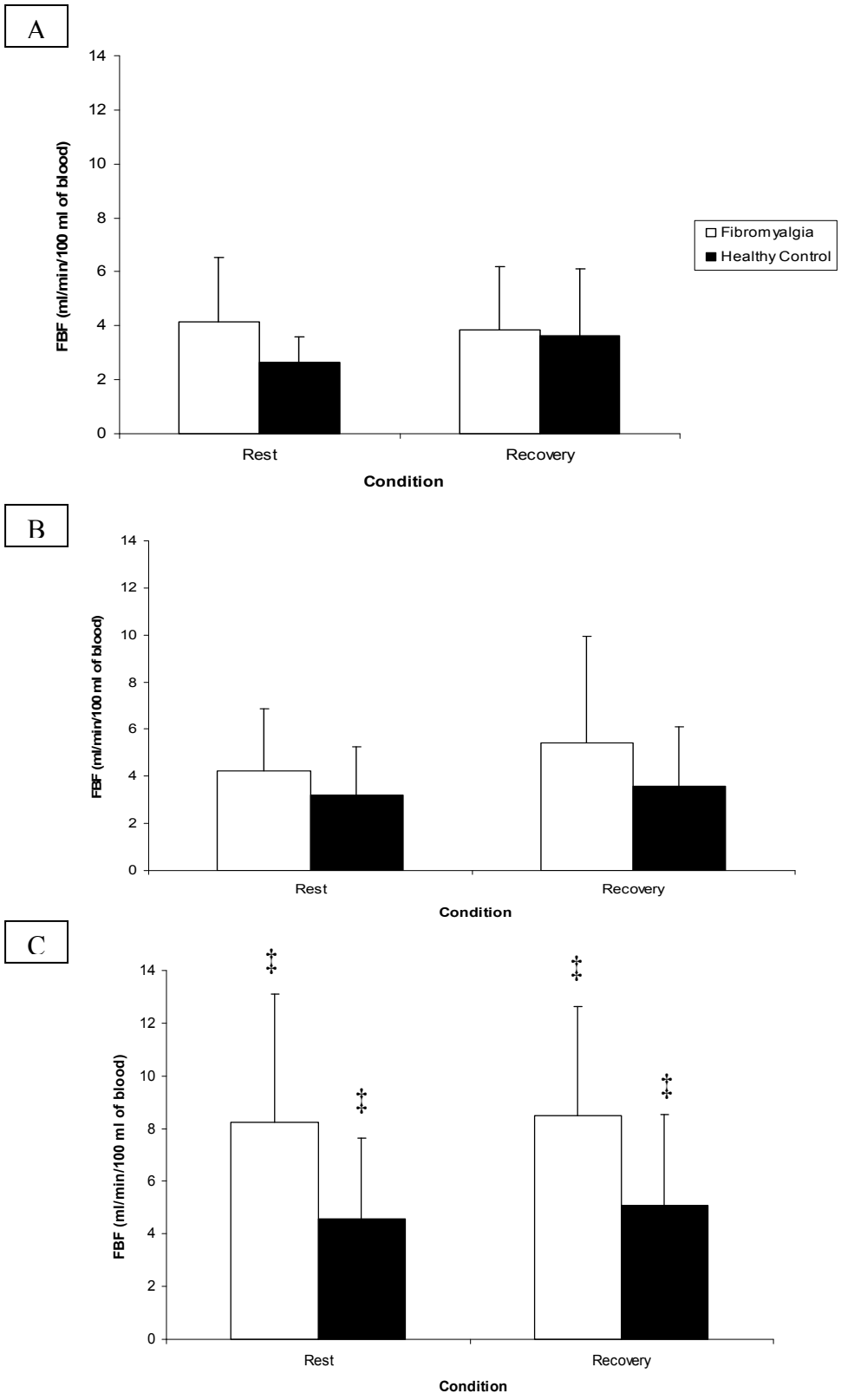


Figure 17. Forearm blood flow at rest and during recovery from acute resistance exercise for A) Pre1, B) Pre2 and C) Post in women with FM (n=9) and HC (n=15). ‡ $p<0.05$, significantly different from Pre1 and Pre2. Values are mean ± SD.

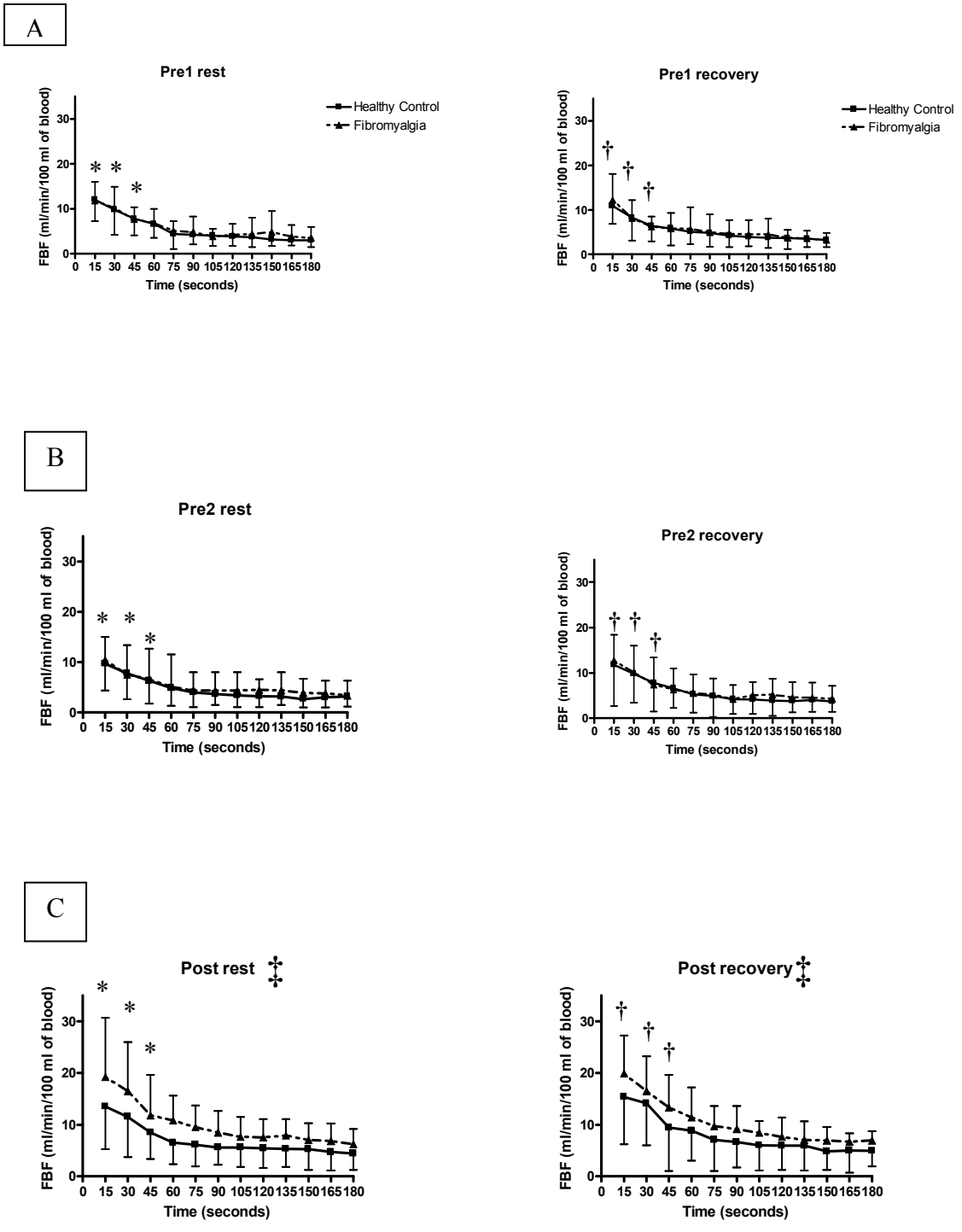


Figure 18. Vasodilatory responsiveness at rest and during recovery from acute resistance exercise for A) Pre1, B) Pre2 and C) Post in women with FM (n=9) (*triangles*) and HC (n=15) (*squares*).*$p<0.05$, significantly different from rest. †$p<0.05$, significantly different from recovery. ‡ $p<0.05$, significantly different from Pre1 and Pre2. Values are mean ± SD.

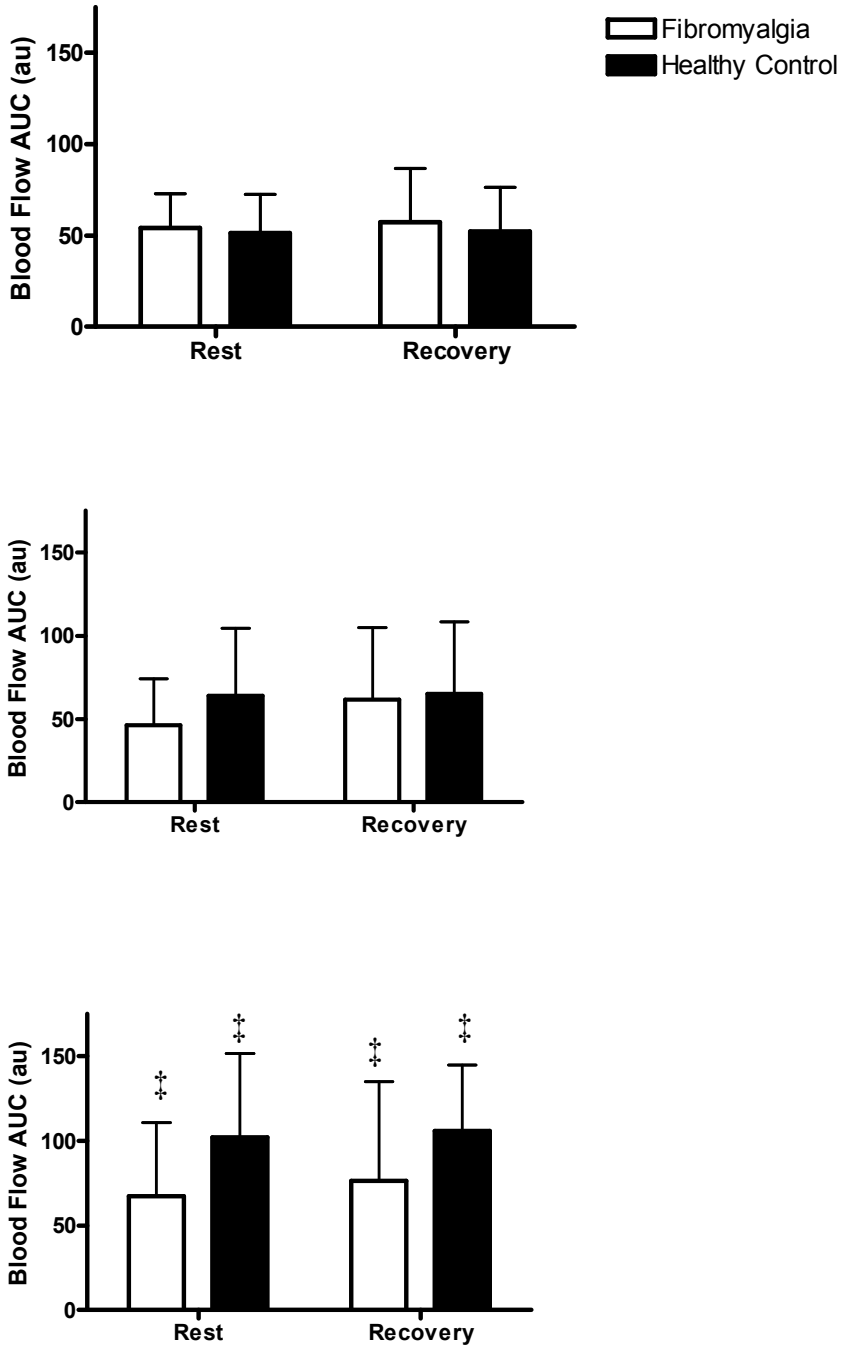


Figure 19. Reactive hyperemia blood flow at rest and during recovery from acute resistance exercise for A) Pre1, B) Pre2 and C) Post in women with FM (n=9) and HC (n=15). ‡ $p<0.05$, significantly different from Pre1 and Pre2. Values are mean ± SD.

CHAPTER 5: DISCUSSION

The main findings of the present study are that RET increases maximal strength in women with FM and HC and decreases FM impact in women with FM. This study also found that there were no differences in autonomic and vascular function between women with FM and HC at Pre1, Pre2 and Post or during rest, the pre-exercise CPT, recovery or the post-exercise CPT. When evaluating the women on autonomic and vascular function before and after RET we found that 1) HR and normalized HRV responses to the post-exercise CPT were elevated above resting levels but not above recovery levels at Pre1, Pre2 and Post, 2) there was a significant increase in HR in response to the post-exercise CPT after RET compared to recovery, 3) 12 weeks of RET attenuated the increase in aortic SBP and MAP in response to the post-exercise CPT before RET, 4) after acute resistance exercise, there were significantly attenuated BP responses to the post-exercise CPT, and 5) RET increases pre-exercise and post-exercise FBF and vasodilatory capacity compared to the untrained state.

Effects of Resistance Exercise Training on Maximal Strength and FM Severity. Women with FM had similar levels of maximal strength as HC before beginning the intervention as well as after RET. This result contradicts previous studies that have shown lower muscular strength in women with FM compared to healthy controls before RET (48, 117, 142). Regardless, in the present study, RET increased maximal strength similarly in both groups of women. In agreement with previous data, the present study indicates that women with FM have the same ability to develop muscular strength as healthy controls (49).

In agreement with current data, there were significant reductions in the total number of active tender points, myalgic score and FIQ in the women with FM after RET. Before RET, the number of active tender points and myalgic score, while sufficient for diagnosis of FM, were lower than what has been reported in other studies (49, 72, 116, 142). In addition, the FIQ scores were lower in the present study compared to previous reports in women with FM (72, 116, 129). In the present study, the number of active tender points was, on average, below the number necessary for diagnosis after RET (less than 11). There was only 1 of the 9 women with FM that would meet the diagnostic criteria for FM based on the number of active number tender points after RET. A recent study by Panton et al. (116) demonstrated a reduction in the number of active tender points, myalgic score and the FIQ following a 16-week RET program. In addition,

a 21 week RET study by Valkeinen et al. (142) in women with FM also noted a significant reduction in the number of active tender points (16.5 to 14.6 units). Rooks et al. (129) found a significant reduction in the FIQ score by 28% in women with FM after 16 weeks of combined RET and aerobic exercise training.

Since the inclusion criteria were so tightly controlled, we recruited a group of highly functioning women with FM. The number of active tender points (13 units) and the myalgic score (14 units) were also lower than subjects used in previous studies. The study by Panton et al. (116) was similar to the present study in that participants began with 14 active tender points and a myalgic score of 18 units. The mean FIQ for our sample was above 50 units (56.8 units), which is about average for an individual with FM, but not for one that is severely impacted (> 70 units). Panton et al. (116) had an initial FIQ of greater than 60 units. In addition, previous studies have also had women with FM that were suffering from multiple comorbidities. In our previous manuscripts, Kingsley et al. (72) and Panton et al. (116, 117), there were participants with hypertension, diabetes and/or obesity. However, in the study by Figueroa et al. (36) there were no comorbidities in the participants, and there was still a significant reduction in the number of active tender points after 16 weeks of RET. There was no control of menstrual age in any of these previous studies, which may have contributed to the different findings of the present study. Since the women in the present study seemed to have lower values of FM impact this could be the reason why we found no differences in baseline strength values.

Acute and Chronic Effects of Resistance Exercise on Autonomic Modulation, Aortic Wave Reflection and Blood Pressure Responses to the CPT. Women with FM were not different to HC when measured for resting HR and parameters of HRV at Pre1, Pre2 and Post or during rest, the pre-exercise CPT, recovery or the post-exercise CPT. This was similar to our recently submitted manuscript in older women (70), in which women with FM and HC had similar resting HR and HRV measurements. Previous studies have shown higher HR, LFnu and LF/HF ratio, as well as lower HFnu in women with FM compared to age-matched controls at rest (19, 38). Both Cohen et al. (19) and Furlan et al. (38) collected data in the supine position. Similar to our recent report (70), data collection in the seated position likely explains the discrepancy in resting HRV between our data and that from previous studies (19, 38). Moving from a supine position to a seated position increases HR via vagal withdrawal. Even though the vagal withdrawal may be

slight, it may have been sufficient enough of a stimulus to eradicate any significance difference compared to previous studies. It is also of importance to note that in the present study the women with FM were not as affected by FM and comorbidities as those in previous studies which could have also influenced our results.

The CPT has been shown to increase sympathetic mediated increases in HR in healthy men and women (12, 100, 135). In the present study, HR and LFnu increased while HFnu decreased in both groups in response to the pre-exercise CPT at Pre1, Pre2 and Post. This response was unexpected in the women with FM. Furlan and others (38) reported no increase in sympathetic activity in women with FM during 75 degrees of head-up tilt compared to rest, suggesting an attenuation of sympathetic activity in response to orthostasis. Similarly, our preliminary data demonstrated no alteration in autonomic modulation during IHG in women with FM compared to HC. This attenuation of sympathetic activity was suggested to result in a reduced sympathetic response during a stressor, such as head-up tilt, IHG or the CPT. The data from the current study are in contradiction with previous data. We demonstrated that when exposed to a pre-exercise CPT, women with FM have similar autonomic modulation of HR as compared to HC. Furlan et al. studied women with FM with an average age of 44 years, disease duration of 7 years, and 14 active tender points, all similar to the present study. There was no mention of medication usage, or body weight. However, Furlan et al. included a group of HC who were 37 years of age. Although, it is not known if there was a significant difference in age between the two groups, it is possible that the age discrepancy in the study by Furlan et al. could contribute to the discrepancy with our findings. Data from Vallejo et al. (143) reported that age was a prime determinant of HRV.

Contrary to previous studies, the women with FM in the present had similar resting BP and BP responses to both of the CPTs as HC (36, 38). Furlan et al. (38) reported that women with FM have augmented levels of BP at rest and a reduced ability to increase BP to orthostasis. Furthermore, a study by Figueroa and others (36) reported that compared to HC women with FM had higher levels of SBP and significantly elevated PP at rest. It has been proposed that there is a reduction in the ability in women with FM to alter BP such that there are attenuated BP responses to physiological stress including orthostasis (38) and the CPT (120, 141). In the present study, women with FM and HC had similar BP and wave reflection responses to the CPT and acute resistance exercise before and after RET. Both Vaeroy et al. and Qiao et al. utilized

women with FM with an average age of 43 years (range 22-61 years) and HC with an average age of 37 (range 22-51 years). In addition, 55% of the women with FM and 41% of the HC were smokers in each of these studies. Smoking is known to increase BP and arterial stiffness at rest and in response to stimuli and may assist in explaining the attenuation in BP seen in both groups. In addition, in both of these studies the water temperature was 4°C, and the duration of the CPT was 1 minute. In the present study, 10°C was utilized for a 2-minute CPT. Mitchell and colleagues (100) examined pain responses to the CPT using 1°C, 3°C, 5°C, and 7°C water. It was concluded that small changes in water temperature can yield drastically different results. The discrepancy in the methodology between these studies and the present study may limit the ability to accurately compare the results.

Aortic wave reflection and BP are increased by the CPT. Casey et al. (12) demonstrated increases in the AIa with concurrent decreases in Tr, a surrogate marker of aortic stiffness, during CPT in healthy young individuals with a return to resting values 180-seconds after the CPT. The increases in the properties of the aortic waveform in the study by Casey et al. (12) were attributed to an increase in aortic MAP, a determinant of arterial stiffness and wave reflection (76). Furthermore, Casey et al. (12) also reported increases in aortic SBP and aortic PP that were attributed to increased myocardial oxygen demand. Geleris et al. (41) noted that the CPT significantly increased the AIa in young healthy men and women. Fennessy et al. (33) reported that the CPT was a sufficient stimulus to significantly increase both SBP and DBP. In the present study, the AIa and AIa@75 were increased during the pre-exercise CPT. However, Tr did not decrease in response to CPT in our middle-aged women with and without FM. In addition, our data demonstrate that the CPT is able to increase the digital and aortic PP in women with FM and HC. Our data suggest that the increases in AIa and AIa@75 are mediated by vasoconstriction caused by the CPT.

While there are multiple reports investigating acute aerobic exercise on HRV (34, 47, 138), only a few studies have investigated the acute effects of resistance exercise (54, 70, 107, 126). Figueroa et al. (34) demonstrated that HF power was decreased compared to resting values at 20 minutes after a 20-minute session of brisk walking in middle-aged women. In healthy young men and women, Heffernan et al. (54) demonstrated that the greater HR observed 30 minutes after an acute resistance exercise bout compared to endurance exercise was due to a greater decrease in parasympathetic modulation. Niemela et al. (107) exercised healthy men at

either 30% 1-RM or 80% 1-RM and that HR did not recover for at least 1 hour. In our recent study (70), we reported an increase in HR and HFnu above resting levels 20 minutes after a full-body acute resistance exercise consisting of 1 set of 10 exercises in women with FM compared to HC. Our data suggest that acute resistance exercise does not alter HR or autonomic modulation in women with or without FM. Unlike other studies, the present study utilized 5 sets of 10 repetitions on the leg press and not a full-body protocol. By using just the leg press, the amount of muscle utilized in the present study was different from our previous study (70), Heffernan et al. (54) and Niemela and others (107). The amount of muscle mass utilized during exercise is directly correlated with sympathetic activity (132, 133). Perhaps the leg press was an insufficient stimulus to alter HR or autonomic modulation in our women.

In the current study, there were significant increases and decreases in digital and aortic PP and DBP, respectively, but no effect of the acute resistance exercise on AIa or Tr. Data have demonstrated that an acute bout of resistance exercise may decrease brachial and aortic BP (53, 86), while others have not (75, 108). MacDonald and others reported a significant decrease in brachial systolic BP from 30-60 minutes of recovery from an acute resistance exercise bout in young women (86). In agreement with our results, Heffernan et al. (53) reported that young resistance-trained men had a decrease in brachial and aortic DBP with no change in SBP following a maximal aerobic test. In addition, Heffernan et al. (53) noted increases in brachial and aortic PP after the maximal aerobic test. Taken together, this may suggest that the responses of digital and aortic BP to exercise, either aerobic or resistance, are augmented following exercise training.

To our knowledge, no study has utilized the CPT after acute resistance exercise. Previous data collected in women with FM have suggested that after 25 minutes of recovery from acute resistance exercise, there is a greater increase in vagal tone in women with FM compared to HC (70). An increase in vagal tone to resting levels may suggest that the autonomic nervous system has fully recovered. Wray and others (147) examined HR responses to a CPT administered during handgrip or knee-extensor exercise in young men. HR increased in response to the CPT compared to either exercise condition. However, Wray et al. (147) also reported an attenuated increase in vascular resistance during the CPT applied during exercise compared to a CPT at rest. These data suggest that sympathetic stimulation induced by a CPT during exercise is different from rest. In a study using male and female patients with cystic fibrosis, Schrage and

colleagues (131) reported that a CPT during forearm exercise increased HR, but vascular resistance did not change. In agreement with previous studies (131, 147), we observed that HR and autonomic modulation did not respond to the post-exercise CPT during the recovery from acute resistance exercise. In the present study, when our participants were exposed to CPT after an acute exercise bout, which is known to increase sympathetic activity (12, 60), there were significant increases in aortic wave reflection (increased AIa and AIa@75 with a decrease in Tr) and DBP compared to resting and recovery measurements. However, digital and aortic SBP, PP, and MAP did not change in response to the post-exercise CPT in women with FM or HC. Perhaps during recovery from acute resistance exercise, sympathetic activation mediated by the post-exercise CPT is able to produce vasoconstriction but not tachycardia in middle-aged sedentary women.

Studies investigating the effects of RET on resting HR and overall HRV are limited. Cooke et al. (23) noted no significant changes in absolute or normalized measures of HRV after 8 weeks of RET in healthy young individuals. Conversely, Figueroa et al. (36) demonstrated that 16 weeks of RET significantly increased total power as well as RMSSD, a measure of parasympathetic cardiac modulation, in women with FM. Although not statistically significant, there was also an improvement in Ln HF power. However, we (36) noted that the improvements in HRV after RET may have been due to autonomic dysfunction before RET. In the present study, the similarity in autonomic modulation in women with FM and HC before RET would explain in part the lack of a training effect.

Those studies examining acute responses of exercise have compared rest to recovery but they have not addressed the effects of RET. Figueroa et al. (34) demonstrated that while 16 weeks of aerobic training had no effect on resting HR and measures of HRV, training significantly improved autonomic modulation following a bout of moderate-intensity aerobic exercise in middle-aged women. Both groups of women had an increase in post-exercise Ln HF and a consequent decrease in HR. In contrast, post-exercise autonomic modulation of HR did not change 20-25 minutes after RET. Our results demonstrate that our RET protocol does not cause the reduced vagal modulation of HR observed after acute resistance exercise in moderate active men (54). To our knowledge, no study has utilized the CPT during the recovery of acute exercise after a period of training. However, Cooke et al. (23) measured sympathetic nerve activity during the valsalva maneuver in young healthy men, which elicited no change in

sympathetic activity after 4 weeks of aerobic training. On the contrary, Lee et al. (77) examined responses to head-up tilt after 2 weeks of aerobic training compared to a control group. They found a reduced effect of the head-up tilt on Ln LF, Ln HF and the Ln LF/Ln HF compared to the control group. Although markers of autonomic modulation of HR after acute exercise did not significantly change after RET, there was an increase in HR during the post-exercise CPT. This response was attenuated by acute resistance exercise before RET; thus, the increase in HR during the post-exercise CPT would indicate increased cardiac autonomic responsiveness to a stimulatory afferent signal after RET.

The effect of RET on resting aortic wave reflection are mixed (11, 13, 25). While the present investigation showed no change in AIa, a study by Cortez-Cooper (25) in young women found that 11 weeks of heavy RET increased the AIa. Meanwhile, Casey et al. (11) demonstrated that 12 weeks of high-intensity RET does not alter the AIa or Tr in young men or women if there is no increase in training volume. Another study by Casey et al. (13) has suggested that 18 weeks of RET has no effect on AIa or Tr in normotensive postmenopausal women. The disparity in the results by these studies may be caused by differences in training protocol, age, sex hormone levels and BMI. The study by Cortez-Cooper et al. (25) utilized a heavy resistance training protocol. In the first 4 weeks of training participants completed 3 sets of 10 repetitions. The following 4-week period consisted of 3 sets of 5 repetitions. During the last 3 weeks of the intervention the intensity was increased by adding timed super-sets for 6 sets of 5 repetitions per exercise. Casey et al. (13) trained participants starting at 50% of their predetermined 1-RM for 1 set of 10 exercises. The current study started training participants at 50-60% of their 1-RM, with each resistance exercise bout consisting of 8-12 repetitions for 5 exercises. It has been shown that aging increases central artery waveforms as measured by AIa (13). It has also been demonstrated that estrogen is cardioprotective and can maintain arterial elasticity (13, 14). Furthermore, increases in BMI have been strongly correlated with decreased arterial compliance, and thus increased aortic wave reflection as measured by AIa. Our participants were not only 10 years younger than participants studied by Casey et al. (13), they were also premenopausal and some were classified as hypertensive, yet the responses to RET were similar. The participants used in our study had an average BMI of 28.9kg/m^2, while Casey et al. (13) had an average of 25.5kg/m^2. Although both sets of participants were classified as overweight, our analyses included obese participants while Casey and others (13) did not.

When addressing the effects of RET on an acute hemodynamic responses to exercise, Heffernan et al. (53) demonstrated that a maximal bout of aerobic exercise increased radial augmentation index (AIx) in resistance trained and sedentary young men. The maximal aerobic exercise did not change Tr for either group. However in the current study, there was no significant increase in wave reflection (no change in AIa, AIa@75 or Tr) during post-exercise CPT after RET. This alteration in response to the postexercise CPT after RET may suggest an improvement in vascular function.

Unlike aerobic exercise training, reductions in brachial and aortic BP do not always occur with RET (4, 6, 7, 16). While studies with IHG training demonstrate reductions in BP, they do so without increasing full-body muscular strength and mass. Circuit weight training has a cardiovascular effect due to the short rest periods and has been shown to reduce HR and BP (69, 83). Carter and colleagues (10) reported that 8 weeks of high-intensity RET decreased brachial BP measurements such as brachial systolic, diastolic and mean arterial BP in young men and women without increasing muscle sympathetic nerve activity. Similarly, Collier and colleagues (21) reported a decrease in brachial SBP after 4 weeks of RET in men and women with mild hypertension. In contrast, Casey et al. (13) demonstrated that 18 weeks of moderate RET in normotensive postmenopausal women had no effect on brachial or central aortic blood pressure. Similar results were reported by Olson and colleagues (113) such that 1 year of RET did not alter brachial SBP or DBP in premenopausal women. Our data are in agreement with Casey et al. (13) and Olson et al. (113) in that no alterations occurred in resting brachial and aortic BP after 12 weeks of RET in women with FM or HC. Our study also found that RET does not affect peripheral and aortic BP responses to CPT and acute resistance exercise.

Acute and Chronic Effects of Resistance Exercise on Forearm Blood Flow and Vasodilatory Capacity. It has been suggested that a reduction in circulation in women with FM may either be caused by augmented sympathetic activity (31, 68, 80), increases in ET-1 (114) or decreases in bioavailability of nitric oxide (31, 68, 80). While some studies have reported greater sympathetic activity in women with FM compared to HC (38, 92, 94) this has not been consistently seen (70). In addition, Pache et al. reported increases in ET-1 in women with FM. The reduced blood flow in women with FM has been attributed to increases in cytokines and reactive oxygen species that limit the production of NO (31, 68). In the present study there were

no differences in FBF or vasodilatory capacity in the women with FM compared to HC across time or condition. In contrast to current data, the present study suggests that vasodilatory capacity is comparable in women with and without FM. In addition, the effects to resistance exercise and RET were comparable between groups for FBF and vasodilatory capacity. Ultimately, more research needs to be conducted to ascertain vascular responsiveness at rest and in response to RET in women with FM.

Those studies using acute aerobic and resistance exercise have shown an increase in FBF during post-exercise recovery compared to pre-exercise in untrained men and women (28, 74). Specifically, Kingwell et al. (74) demonstrated that FBF was increased 1 hour after cycling at 65% of VO_2 max for 30 minutes. Fahs and colleagues demonstrated that in young men, FBF and vasodilatory capacity were elevated above rest 25 minutes after 80% 1-RM for 4 sets on the bench press and 70% 1-RM for 4 sets on the biceps curl. A study by DeVan et al. (28) demonstrated that an acute bout of resistance exercise consisting of 1 set of 8-12 repetitions at 50% 1-RM, and 1 set to failure at 75% 1-RM for nine exercises decreased carotid arterial compliance for 30 minutes. In the current study, there was no alteration of peripheral blood flow or vasodilatory capacity 15 minutes after acute resistance exercise. The recovery of FBF to baseline after RH differs among the present study and previous reports (Fahs et al.(32) and DeVan et al.(28)) which may be due to the differences in the protocols used. Fahs et al. (32) utilized young healthy men and a high-intensity (70-80% 1-RM) resistance load for the upper body. DeVan et al. (28) quantified alterations in central carotid blood flow, whereas we assessed changes in peripheral FBF. It may be possible that the ability to increase FBF was reduced because we used a lower body resistance exercise protocol. However, the protocol in the present study has been shown to be tolerable in women with FM (49, 142).

Alterations in FBF and vasodilatory capacity have been found to occur after exercise training (4, 16, 29, 56, 97, 124). It has been shown that aerobic exercise (56), combined aerobic and anaerobic exercise (16), and handgrip exercise training (3, 97) are effective interventions to improve resting vasodilatory capacity. In studies utilizing full body RET, Rakobowchuk et al. (124) demonstrated that 12 weeks of RET increased resting vasodilatory capacity in young healthy men without altering flow-mediated dilation of the artery. Other studies have also reported no change in flow-mediated dilation after RET in young men and women (11) and older postmenopausal women (13). Regardless, the data in the present study demonstrated that 12

weeks of RET improved resting FBF and vasodilatory capacity in premenopausal women with FM and HC. This finding is in agreement with that of Olson et al (113), who found an increase in resting brachial flow-mediated dilation after 1 year of moderate intensity RET in overweight premenopausal women. The difference between the present study and Casey et al. (13) may stem from the age difference and hormonal status of the participants. We utilized participants that were a decade younger than Casey et al. (13). Estrogen has been shown to have cardioprotective effects and to maintain endothelial function, which may also explain the differences in the results (51, 96, 106). Casey et al. (13) utilized a different method of measurement for FBF (ultrasound versus venous occlusion plethysmography) which limits the ability to compare results. It is feasible that the premenopausal participants in the present study had different baseline endothelial function compared to those from Casey et al. (13).

Studies have only speculated about mechanisms responsible for changes of the arterial vascular system following RET (13, 97, 124). Structural and functional components comprise the elastic properties of the arterial wall. The structural component is derived from the ratio of elastin to collagen and intima-media thickness. The functional component of the arterial wall stems from the smooth muscle tone regulated by the endothelium. After RET, Rakobowchuk et al. (124) reported increases in resting FBF and vasodilatory capacity without concomitant increases in flow-mediated dilation, similar to those of Casey et al.(13). These studies demonstrate improvements in arterial diameter, without improving brachial vascular endothelial function. It is well documented that arterial BP can increase as high as 320/250 mmHg during acute resistance exercise (6, 7, 69). Over time, these acute, intermittent increases in arterial BP may result in structural and functional alterations of the endothelium (7, 13, 97, 124). Structural alterations that have been proposed to occur after RET may include a reduction in intima-media thickness, but the data are extremely limited to support this conclusion (124). A more likely explanation is that frequent increases in shear stress mediated by reactive hyperemia in response to the resistance exercise may stimulate functional changes within the endothelium, similar to aerobic training (124). Specifically, increases in NO bioactivity/bioavailability or other structural changes are necessary in order to maintain peak shear rate (97, 124). Functional changes such as increases in sympathetic vasomotor tone or increased levels of other vasoconstrictive peptides (ET-1, vasopressin) caused by RET may also explain alterations of the endothelium after RET (7, 13, 97, 124). However, the one study that has evaluated these

peptides after RET has demonstrated little or no change (7). Therefore, more studies need to be completed in order to understand the alterations in response to RET on vasoactive substances and their effect on the vasculature.

To our knowledge, there is only one study that has utilized acute resistance exercise before and after RET. Copeland et al. (24) examined responses of FBF to acute isometric handgrip exercise before and following 3 weeks of RET and found a significant increase in FBF immediately following acute isometric handgrip compared to an aerobic training group. While the present study utilized isotonic resistance exercise instead of isometric, we were unable to demonstrate an increase in FBF in women with FM and HC 15 minutes after exercise. The inability to increase FBF with acute exercise in the present study could be explained by the size and location of muscle mass recruited (forearm vs. thigh) and the time of recovery (immediate vs. 15 min). Interestingly, it is important to note that in the present study, even though it was not different from the pre-exercise FBF, the post-exercise FBF was still greater in magnitude when compared to the control period after RET. This suggests the full-body RET was a sufficient stimulus to increase FBF, both at rest and post-exercise.

It is important to note that the present study has a small sample size which may reduce the ability to interpret the results. In addition, women with FM were only taking sleep aids. Other researchers have noted that the medication being taken by women with FM may limit the ability to draw conclusions from their results. Based on previous reports, the average woman with FM takes between 8-12 different medications a day (42). The women with FM in the present may not have been as impacted by their FM as in previous studies. Although the FIQ scores in the present study suggest moderately impacted participants, we controlled for many comorbidities. In addition, there was no control of the menstrual cycle in the present study. All participants were premenopausal and none were taking exogenous estrogen. Leicht et al. (78) demonstrated that HRV was not affected by different stages of the menstrual cycle. While it has been demonstrated that estrogen may influence aortic wave reflection the data are inconclusive (106). It has been demonstrated that estrogen increases endothelium-independent and dependent alterations of the vasculature. Specifically, as estrogen levels increase there is a rapid release of NO as well as greater bioavailability of NO within the endothelium. Chan et al. (14) have suggested that at midcycle (days 10-13), when estrogen is high, there is an augmentation of endothelium-dependent vasodilation. In addition, Chan and others (14) note that estrogen

increases the number and sensitivity of the vasoconstrictive alpha-adrenergic receptors and also increases synthesis of norepinephrine. This suggests that estrogen has a direct effect on sympathetic activity, and therefore indirectly has effects on the forearm resistance vessels. The present study utilized a leg exercise for the acute protocol, which may have been an insufficient stimulus to increase FBF. However, it is important to note that post-exercise FBF was elevated after RET compared to the control period, thereby suggesting a systemic effect. While some of the participants were classified as Stage 1 hypertensives, none were taking any medication to control their blood pressure. It is possible that the higher blood pressures may have had a greater magnitude of change in response to the acute and chronic resistance exercise. Furthermore, although there were no statistical group differences in BMI, women with FM were closer to being obese, while HC were on the lower end of being overweight. While studies examining vasodilatory capacity have more frequently used ultrasound to determine flow-mediated dilation, we utilized venous occlusion plethysmography. Venous occlusion plethysmography has been shown to have good repeatability and is a valid measurement of resistance artery function (46, 55); ultrasound focuses on large conduit arteries (46). It is important to note that vasodilatory capacity was reduced in both groups of participants compared to previously published data (4, 55). It is possible that all participants in the current study had some level of endothelial dysfunction at study entry, thus allowing for a greater increase in vascular responsiveness (29).

CHAPTER 6: SUMMARY, CONCLUSIONS AND FUTURE DIRECTIONS

Summary

Women with FM have been shown to have reductions in muscular strength and endurance and demonstrate autonomic and vascular dysfunction at rest. Furthermore, women with FM have an inability to alter autonomic modulation in response to a physiological stimulus, such as the cold pressor test. Current research on the effects of resistance exercise in women with FM is limited. Those studies that have shown improvements in FM severity have done so without knowing the mechanisms. In addition, only a few studies have investigated the effect of resistance exercise on the autonomic dysfunction noted in women with FM. There have been no studies that have investigated the vascular dysfunction in women with FM. Regardless, it has been demonstrated that women with FM respond favorably to resistance exercise training. Therefore, the purpose of the present study was to 1) evaluate the effects of RET on FM severity, 2) to elucidate autonomic modulation, vascular activity, and BP at rest, during the CPT and after acute resistance exercise prior to and following 12 weeks of RET in women with FM compared to HC and 3) to evaluate FBF and vasodilatory responses at rest and in response to acute resistance exercise before and after 12 weeks of RET in women with FM compared to HC.

Twenty-nine women were recruited from the Tallahassee area and agreed to participate in the study. Women were classified as either diagnosed with FM (n=9) or as a HC (n=20). The study's protocol required the participants to undergo a series of tests at baseline, following a 4-week control period and after 12 weeks of RET. These tests included tender point assessment for reactivity and sensitivity, FM impact, and maximal strength. Acute responses to resistance exercise included HR, HRV, aortic wave reflection, aortic and digital BP, FBF and vasodilatory capacity. Each group underwent a 4-week control period in which they were asked not to change their current habits and 12 weeks of RET for 3 sets per 5 exercises starting at 50-60% of their 1-RM for upper and lower body, respectively.

Conclusions

First, it can be concluded that the addition of a resistance exercise training program is well tolerated in women with FM. There was no difference at the beginning of the study between participants for any of the collected variables, nor were there differences after RET.

The following is a summary of the significant findings and how they relate to the original hypotheses and predictions.

Two of the 3 original hypotheses were accepted. Women with FM had improvements in maximal strength that decreased the severity of their FM so this hypothesis is accepted. There was no effect of RET on autonomic modulation which resulted in no change in BP or aortic wave reflection therefore this hypothesis must be rejected. RET increased FBF and vasodilatory capacity in women with FM so this hypothesis was accepted.

Four of the original 15 predictions that were proposed for the current study were accepted. The accepted predictions were the following: 1) the number of active tender points was reduced following the 12 weeks of RET in the women with FM, 2) there was a reduction in the myalgic score in the women with FM after RET, 3) the FIQ decreased after RET in women with FM, and 4) the increases in maximal strength were similar between women with FM and HC after RET. In contrast, the data showed no sympathetic overactivity in women with FM compared to HC at rest, nor did it demonstrate attenuation in autonomic modulation during the CPT or after the acute resistance exercise before RET. Furthermore, there was no difference between the groups at Pre1, Pre2 or Post. Therefore, these predictions must be rejected. The results from the present study also showed no differences in aortic wave reflection at any time point during any condition between women with FM and HC, thereby we must reject these predictions. In addition, there were no differences between groups in vascular activity at Pre1, Pre2 or Post. There were also no differences before or after the acute bout of resistance exercise. Therefore, these predictions must also be rejected. There was also no difference between groups for FBF or vasodilatory capacity at any time point either before or after acute resistance exercise. Therefore, we must also reject these predictions. However, the full-body RET was a sufficient stimulus to increase FBF, both at rest and post-exercise. Enrollment in this study was tightly controlled for both groups. Unlike previous reports, the women with FM in the present also had no comorbidities. While this limits the ability to compare results among studies, it does demonstrate that when inclusion parameters are tightly controlled women with FM respond similarly to HC to these variables.

In conclusion, the findings of the present study suggest that RET can decrease FM severity in women with FM. After RET, only 1 of the 9 participants would meet the criteria necessary for diagnosis of FM. In addition, the results demonstrate that 12 weeks of RET can

increase FBF and vasodilatory capacity in premenopausal women with or without FM. It is possible that the reduction in FM symptoms may be associated with the improvement in blood flow and muscle strength; however, confirmation of this hypothesis deserves further investigation. Overall, this study suggests that RET is a useful modality for treating FM.

Future Directions

Based on the results of the present study there are many areas for future research. While the data suggest that resistance exercise has no effect on autonomic modulation, aortic wave reflection, and BP in women with FM compared to HC, these data are exploratory. Much of the research on these topics is limited in healthy participants, not to mention women with FM.

Currently, studies have reported alterations in autonomic modulation and vascular dysfunction at rest in women with FM compared to HC. However, the data from the present study do not support these findings. While the present study had a small sample size, the two groups were matched for age, height, weight and BMI. Other studies have utilized control groups that were younger and do not report participants characteristics. It has been reported that women with FM tend to have higher BMI's than matched HC. In the present study, BMI was matched between the two groups which may have reduced the differences that have been seen in other studies between women with FM and HC. Future research needs to address the issue of BMI when recruiting participants. Including an overweight group and a separate obese group of women with FM compared to match HC may increase understanding of FM.

It is also important to evaluate the effects of resistance exercise on autonomic modulation, aortic wave reflection, BP, FBF and vasodilatory in women with FM. In addition to the present study, numerous other researchers have demonstrated that resistance exercise is a valuable tool for treating FM. If autonomic dysfunction is involved in the etiology of FM, the effects of resistance exercise on autonomic function is important to understand. We previously evaluated one set of 11 exercises on acute autonomic modulation in women with FM compared to HC and found different results from the current study on measures of autonomic modulation. Similarly, we examined 16 weeks of RET on women with FM and reported different results than the current study for autonomic modulation. Therefore, future research needs to determine the most appropriate exercise prescription in women with FM. For example, does an acute bout of resistance exercise affect autonomic modulation using 1 set of 11 exercises differently than using

3 sets of 5 exercises in women with FM compared to HC? Does RET using these different prescriptions alter autonomic modulation in a different manner? Is there an effect of duration, either 12, 16 or 21 weeks, on autonomic modulation in women with FM? What is the time course of detraining on autonomic modulation in women with FM compared to HC?

The effects of resistance exercise on aortic wave reflection, BP, FBF and vasodilatory capacity have implications in women with FM and in HC. The data in both sets of participants are limited. In healthy women, it has been advised that RET be included as part of a healthy lifestyle. However, the effects of resistance exercise on these variables are mixed. Different testing protocols make interpretation of the results difficult. Again, which exercise prescription is necessary for women with FM? Is it different than HC? Does time of training make a difference? What is the time course of detraining in women with FM compared to HC? These are important questions that need to be addressed.

More data are needed on the effects of a physiological stressor in women with FM, besides resistance exercise. In the present study, the CPT was used as the stressor. Perhaps the temperature used in the CPT was not a sufficient stimulus. Other modalities that could be useful would be orthostasis or isometric hand grip. A reduction in autonomic modulation in these women tends to manifest itself during standing. Most of the data on autonomic modulation in women with FM has focused on orthostatic alterations in women with FM. However, there have been no studies that have examined the orthostatic response before or after acute or chronic resistance exercise. Therefore, a study investigating the effects of resistance on orthostasis in women with FM compared to HC may have large implications. In addition, the responses to a physiological stressor after resistance exercise in healthy women are missing. Does an acute bout of resistance exercise alter autonomic modulation, aortic wave analysis and BP in women with FM compared to HC? Does RET alter these effects?

In addition, there are other variables that may yield valuable insight in FM that have yet to be reported. Only one study has examined vasoactive peptides in women with FM. Pache et al. reported that women with FM have increased levels of ET-1, a potent vasoconstrictor. This study was a pilot study and only utilized a small sample of participants. Other variables may include markers of inflammation such as C-reactive protein or interleukins. It has not been reported whether or not women with FM have full-body inflammation. In addition, even though the present study and others demonstrate that women with FM respond favorably to RET, it

would be interesting to know if RET causes more muscle damage in women with FM than HC? Examination of creatine kinase levels and other markers of muscle damage may offer insight.

Overall, more research on FM is necessary to expand the existing literature. Large longitudinal studies with ample sample size are needed. Current studies in women with FM are plagued by high drop-out rates resulting in small sample sizes. Large longitudinal studies to evaluate the most appropriate modality, frequency, intensity and volume of training are necessary.

APPENDIX A: IRB APPROVAL

Florida State
UNIVERSITY

Office of the Vice President For Research
Human Subjects Committee
Tallahassee, Florida 32306-2742
(850) 644-8633· FAX (850) 644-4392

REAPPROVAL MEMORANDUM

Date: 2/14/2008

To:
James Kingsley
MC 1493

Dept.: **NUTRITION FOOD AND MOVEMENT SCIENCES**

From: **Thomas L. Jacobson, Chair**

Re: **Reapproval of Use of Human subjects in Research:**
The Effects of Resistance Exercise in Women with Fibromyalgia

Your request to continue the research project listed above involving human subjects has been approved by the Human Subjects Committee. If your project has not been completed by 2/12/2009 please request renewed approval.

You are reminded that a change in protocol in this project must be approved by resubmission of the project to the Committee for approval. Also, the principal investigator must report to the Chair promptly, and in writing, any unanticipated problems involving risks to subjects or others.

By copy of this memorandum, the Chairman of your department and/or your major professor are reminded of their responsibility for being informed concerning research projects involving human subjects in their department. They are advised to review the protocols of such investigations as often as necessary to insure that the project is being conducted in compliance with our institution and with DHHS regulations.

Cc: Arturo Figueroa
HSC No. 2008.0004-R

APPENDIX B: INFORMED CONSENT

INFORMED CONSENT FORM

1. I freely and voluntarily and without element of force or coercion, consent to be a participant in the research project entitled "The effects of resistance exercise training on pain, autonomic and endothelial function in women with fibromyalgia." Derek Kingsley, M.S., Arturo Figueroa-Galvez, M.D., Ph.D, a doctoral candidate and a faculty member, are conducting this research project respectively, at Florida State University in the Department of Nutrition, Food and Exercise Sciences.

2. The purpose of the proposed study is to examine the effects of 12-weeks of resistance exercise training on pain and cardiovascular function in women who have been diagnosed with Fibromyalgia. Twenty healthy women and 20 women diagnosed with Fibromyalgia, between 35-50 years of age, will be recruited for this study.

3. My participation in this project will involve coming to the Clinical Exercise Physiology Laboratory at Florida State University on six different occasions before and after resistance training to undergo the following tests described below. These tests should take 2 to 3 weeks to complete.

On the first visit I will be oriented to the study and will be given an informed consent to sign and a form to take to my physician to sign for approval for me to participate in the study and to verify my diagnosis of Fibromyalgia. These forms will need to be returned when I come for my second visit. The first visit should take approximately one hour. I can not participate in this study if I have participated in resistance and/or endurance exercise training on a regular basis for the last 6 months, a recent smoking history (quit within the past 6 months), uncontrolled hypertension (resting systolic blood pressure $\geq$ 160 mmHg and/or diastolic blood pressure $\geq$ 100 mmHg), pregnancy, hypothyroidism, severe depression, previous pituitary disease, diabetes mellitus, active heart disease, history of cancer, coronary artery disease, vascular diseases, a body mass index (BMI) less than 25 kg/m^2 or greater than 30 kg/m^2, or taking any medications that would alter ANS function or endothelial function.

On the second visit I will have my tender point sensitivity evaluated by a certified Rheumatologist. The Rheumatologist will apply pressure with his hands on 18 areas that will include the back of the neck, shoulders, hips, legs, and the front of the neck, shoulders, elbows, and knees. I will tell the Rheumatologist whether these areas are sensitive or sore with touch. This visit should take approximately 30 minutes.

On the third visit I will complete questionnaires and have my upper and lower body maximal strength measured. I will complete questionnaires on demographics, health history, tobacco history, physical activity, quality of life, and pain indices. After completion of the questionnaires my height, weight, blood pressure will also be assessed. Height and weight will be assessed using a standardized scale for the calculation of body mass index. Blood pressure will be measured in a quiet room after I have been seated for a period of 5 minutes. Maximal strength will be measured on the chest press, leg extension, seated row, leg press, and leg flexion. I will be given a warm-up before testing. Once the warm-up is complete, I will be progressed towards a maximal weight that I can lift one time through a full range of motion (1-RM). All measurements will be recorded within 3-5 attempts.

On the fourth visit, following a minimum of 72 hours from the previous, I will return and the 1-RMs will be verified. The highest measurement for the upper and lower body from the two days of testing will be considered the 1-RM. These two visits will take approximately 90 minutes total.

On the fifth visit I will undergo testing to assess my endothelial function. Endothelial function will be measured by occlusion of the brachial artery and a blood draw for endothelin-1 (ET-1). Measurement of ET-1 will be done by collecting venous plasma samples by inserting a needle in the antecubital vein. The blood draw will be done by a trained phlebotomist. After 20 min of supine rest, a blood pressure cuff will be rapidly inflated to 100 mmHg above systolic blood pressure to occlude the circulation for 5 minutes. Immediately following sudden deflation of the cuff, changes in blood flow will be measured continuously for 3 minutes. Following this test, I will undergo a resistance exercise protocol. The protocol will consist of 5 sets of 10 repetitions on the leg press. Two minutes of rest will be given between each set (49). If the individuals are unable to complete the required number of repetitions the weight will be reduced. After 10 minutes of recovery, heart rate (HR) and blood pressure (BP) will be assessed for 5 minutes. At 15 minutes post-exercise the procedures will be repeated.

One week later, on the sixth visit, my autonomic function will be evaluated using heart rate variability (HRV) and blood pressure variability (BPV) and baroreflex sensitivity (BRS) during the cold pressor test. Non-invasive techniques will be used to assess alterations in autonomic function. HR will be obtained from one lead electrocardiogram (ECG). BP will be continuously monitored using a cuff attached to a finger. HRV and BPV will be analyzed from the ECG and BP signals, respectively. Autonomic measures (HRV, BPV, and BRS) will be obtained by using special software. Prior to cold-water immersion I will sit for a period of 10 minutes. The cold pressor test consists of the immersion of the dominant hand in cold water (~10°C) for 2 minutes. The cold pressor test will be repeated following the previously mentioned resistance exercise protocol.

After I complete all testing I will undergo a 4-week control period. After this 4-week period I will undergo the above stated procedures before beginning the resistance training intervention.

After the second bout of testing is complete I will begin resistance training. I will perform 3 sets of 8-12 repetitions twice a week on 5 resistance exercises for the lower and upper body. I will begin training at approximately 50%-60% of my 1-RM and will slowly be progressed throughout the 12 weeks. Once 12 repetitions are completed with proper form the weights will be increased by 2-12% for upper and lower body, respectively. The duration of each exercise session will be approximately 30 minutes. Before and after my workout I will perform 5 minutes of warm-up and cool-down.

4. I understand there is a possibility of a minimal level of risk involved if I agree to participate in this study. The risks will be minimized by using trained technicians and by teaching me proper techniques in testing and training. I will complete a medical history before I can participate in the study. I can not participate in this study if I have participated in resistance and/or endurance exercise training on a regular basis for the last 6 months, a recent smoking history (quit within the past 6 months), uncontrolled hypertension (resting systolic blood pressure ≥ 160 mmHg and/or diastolic

blood pressure ≥ 100 mmHg), pregnancy, hypothyroidism, severe depression, previous pituitary disease, diabetes mellitus, active heart disease, history of cancer, coronary artery disease, vascular diseases, a body mass index (BMI) less than 25 kg/m^2 or greater than 30 kg/m^2, or taking any medications that would alter ANS function or endothelial function.

There are minimal risks or discomforts with answering the enclosed questionnaires. I may choose not to complete the questionnaires and will still be able to participate in the study.

I might experience some muscle soreness from strength testing and training. Care will be taken to try and minimize soreness by thoroughly stretching. There are little data on the injury rate in strength training. Previous experience with strength testing and training in older individuals indicates that the musculoskeletal injury rate is low during strength training.

Evaluation of tender points by the rheumatologist may be painful. This procedure is done routinely for the diagnosis of FM. I should be familiar with this test if I have been previously diagnosed with FM.

The risks of drawing blood are small; there may be some discomfort at the site of needle placement with possible bruising, swelling or infection. The risk will be minimized by the use of skilled technicians using sterile techniques and equipment.

Measurement of forearm blood flow, pain perception and autonomic function may result in discomfort, but the risks are minimal. I may experience discomfort or moderate pain localized to the hand localized during measurement of forearm blood flow and the cold pressor test. I may also experience a drop in blood pressure during the cold pressor test, resulting in headaches, dizziness, or lightheadedness. These possible side effects will disappear within a few minutes after the termination of these tests. If not, I will inform the investigator. I will then lie down on the table on my back with my feet elevated to restore my blood pressure. Pain perception will be assessed through the use of a visual analog scale (VAS).

5. The possible benefits of my participation in this research project include learning about my disease and how exercise affects Fibromyalgia. I will also be given a number of tests free of charge and the results will be given to me and my physician if I wish. I will also be given incentive prizes for participating in the study and completing the study.

6. The results of this research study may be published but my name or identity will not be revealed. Information obtained during the course of the study will remain confidential, to the extent allowed by law. My name will not appear on any of the results. No individual responses will be reported. Only group findings will be reported in publications. Confidentially will be maintained by assigning each subject a code number and recording all data by code number. The only record with the subject's name and code number will be kept by the co-investigator, Dr. Arturo Figueroa, in a locked drawer in his office. Data will be kept for 10 years and then destroyed.

7. In case of an injury first aid will be provided to me by the laboratory personnel working on the research

project any other treatment or care will be provided at my expense.

8. I will not be paid for my participation in this research project but I will be given incentive prizes such as at-home exercise equipment and t-shirts.

9. Any questions I have concerning the research study or my participation in it, before or after my consent, will be answered by the investigators or they will refer me to a knowledgeable source. I understand that I may contact Derek Kingsley on his mobile (850) 322-5053 for answers to questions about this research project or my rights. Group results will be sent to me upon my request.

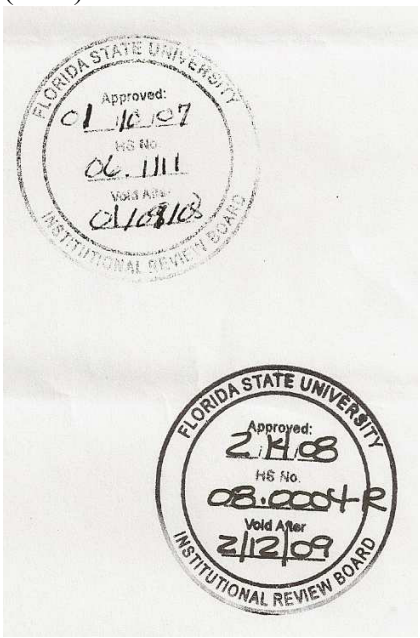
10. In case of injury, or if I have questions about my rights as a subject/participant in this research, or if I feel I have been placed at risk, I can contact the chair of the Human Subjects committee, Institutional Review Board, through the Office of the Vice President for Research, at (850) 644-8633.

11. The nature, demands, benefits and risks of the project have been explained to me. I knowingly assume any risks involved.

I have read the above informed consent form. I understand that I may withdraw my consent and discontinue participation at any time without penalty or loss of benefits to which I may otherwise be entitled. In signing this consent form, I am not waiving my legal claims, rights or remedies. A copy of this consent form will be given to me.

_____

(Subject) (Date)



APPENDIX C: HEALTH HISTORY QUESTIONNAIRE

CARDIOVASCULAR HISTORY

ID# _____
DATE _____

Answer the following questions, indicating the month and year of the event or diagnosis where appropriate.

		Yes	No	Month/Year
1.	Has a doctor ever told you that you have heart disease?	___	___	____/____
2.	Have you ever had a heart attack?	___	___	____/____
3.	Have you ever had chest pain?	___	___	____/____
4.	Have you ever had cardiac catheterization?	___	___	____/____
5.	Have you ever had balloon angioplasty?	___	___	____/____
6.	Have you had coronary artery bypass graft surgery?	___	___	

If yes, list date and number of grafts:

____/____ # grafts: ___ 1 ___ 2 ___ 3 ___ 4^{+}
Mo. Yr.

7.	Have you ever had a stroke?	___	___	____/____
8.	Do you have hypertension (high blood pressure)?	___	___	____/____

If yes, how long have you had hypertension?

_____ less than 1 year
_____ 1-5 years
_____ 6-10 years
_____ more than 10 years

9.	Do you have diabetes mellitus?	___	___	____/____

Health History – continued

		Yes	No	Month/Year
10.	Do you take insulin for diabetes?	___	___	
	If yes, how long have you taken insulin?			
	_____ less than 1 year _____ 1-5 years _____ 6-10 years _____ more than 10 years			
11.	Do you take oral hypoglycemics for diabetes?	___	___	
12.	Do you have a cardiac pacemaker?	___	___	
	If yes, how long have you had a cardiac pacemaker?			
	_____ less than 1 year _____ 1-5 years _____ 6-10 years _____ more than 10 years			
13.	Have you had a carotid endarterectomy?	___	___	____/____
14.	Has your doctor ever told you that you have a heart valve problem?	___	___	____/____
15.	Have you had heart valve replacement surgery?	___	___	____/____
	If yes, what heart valves were replaced?	___ mitral	___ aortic	
16.	Have you had cardiomyopathy?	___	___	____/____
17	Have you had a heart aneurysm?	___	___	____/____
18.	Have you had heart failure?	___	___	____/____
19.	Have you ever suffered cardiac arrest?	___	___	____/____
20.	Do you still have your menstrual cycle?	___	___	____/____
	If yes, when was your last cycle?			

Health History - continued

	Yes	No
21. Is your menstrual cycle painful?	___	___

If yes, please rate on scale (0=no pain, 10= most imaginable pain)

0 1 2 3 4 5 6 7 8 9 10

21. OTHER MEDICAL PROBLEMS: Indicate if you have had any of the following medical problems:

Past	Now	
____	____	Alcoholism
____	____	Allergies
____	____	Anemia
____	____	Arthritis
____	____	Asthma
____	____	Back injury or problem
____	____	Blood clots
____	____	Bronchitis
____	____	Cirrhosis
____	____	Claudication
____	____	Elbow or shoulder problems
____	____	Emotional disorder
____	____	Eye problems
____	____	Gall bladder disease
____	____	Glaucoma
____	____	Gout
____	____	Headaches
____	____	Hemorrhoids
____	____	Hernia
____	____	Hip, knee, or ankle problems
____	____	Intestinal disorders
____	____	Kidney disease
____	____	Liver disease
____	____	Lung disease
____	____	Mental illness
____	____	Neck injury or problem
____	____	Neuralgic disorder
____	____	OB/GYN problems
____	____	Obesity/overweight
____	____	Osteoporosis
____	____	Parkinson's disease
____	____	Phlebitis
____	____	Prostate trouble
____	____	Rheumatic fever

Health History - continued

____	____	Seizure disorder
____	____	Stomach disease
____	____	Thyroid disease
____	____	Tumors or cancer - List type: _____
____	____	Ulcers
____	____	Other - specify: _____

List medications you are taking below:

Name of Drug	Dosage	Times/day	Duration of drug use
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

APPENDIX D: FIBROMYALGIA IMPACT QUESTIONNAIRE

FIBROMYALGIA IMPACT QUESTIONNAIRE (FIQ)

Name: _____ Date: / /

Directions: For questions 1 through 11, please circle the number that best describes how you did

overall for the *past week*. If you don't normally do something that is asked, cross the question out.

Were you able to:	Always	Most	Occasionally	Never
Do shopping? ……	*0*	*1*	*2*	*3*
Do laundry with a washer and dryer?	*0*	*1*	*2*	*3*
Prepare meals?	*0*	*1*	*2*	*3*
Wash dishes/cooking utensils by hand?.....	*0*	*1*	*2*	*3*
Vacuum a rug?.....	*0*	*1*	*2*	*3*
Make beds?	*0*	*1*	*2*	*3*
Walk several blocks?	*0*	*1*	*2*	*3*
Visit friends or relatives?	*0*	*1*	*2*	*3*
Do yard work?.....	*0*	*1*	*2*	*3*
Drive a car?	*0*	*1*	*2*	*3*
Climb stairs?	*0*	*1*	*2*	*3*

12. Of the 7 days in the past week, how many days did you feel good?

0 1 2 3 4 5 6 7

13. How many days last week did you miss work, including housework, because of fibromyalgia?

0 1 2 3 4 5 6 7

(continued)

FIBROMYALGIA IMPACT QUESTIONNAIRE (FIQ) – page 2

Directions: For the remaining items, mark the point on the line that best indicates how you felt overall
for the past week.

14. When you worked, how much did pain or other symptoms of your fibromyalgia interfere with your ability to
do your work, including housework?

●___I___I___I___I___I___I___I___I___I___●
No problem with work Great difficulty with work

15. How bad has your pain been?

●___I___I___I___I___I___I___I___I___I___●
No pain Very severe pain

16. How tired have you been?

●___I___I___I___I___I___I___I___I___I___●
No tiredness Very tired

17. How have you felt when you get up in the morning?

●___I___I___I___I___I___I___I___I___I___●
Awoke well rested Awoke very tired

18. How bad has your stiffness been?

●___I___I___I___I___I___I___I___I___I___●
No stiffness Very stiff

19. How nervous or anxious have you felt?

●___I___I___I___I___I___I___I___I___I___●
Not anxious Very anxious

20. How depressed or blue have you felt?

●___I___I___I___I___I___I___I___I___I___●
Not depressed Very depressed

APPENDIX E: AUTONOMIC FUNCTION TESTING

Autonomic function in fibromyalgia.

Date_____

Subjects ID#_____ control_____ pre_____ post_____

Age_____ Height_____ Weight _____

Last meal _____ Last medication _____

Room temperature _____

Rest: manual BP _____
15 min no recording (instrumentation) Hand_(L or R)_____Finger____

Cuff ____

Rest, file (-1) _____

5 min (paced breathing): HR _____ BP ___comments_____

2 min CP HR _____ BP ___comments_____

Pain before_____ during CPT _____

Water temp _____

Resistance exercise session: comments_____

Post-exercise recovery, file (-2)_____

10 min no recording (instrumentation)

Rest, file (-1) _____

10-15 min (paced breathing): HR _____ BP ___comments_____

20-25 min (paced breathing): HR _____ BP ___comments_____

2 min CP HR _____ BP ___comments_____

Pain before_____ during CPT _____

Water temp _____

APPENDIX F: ENDOTHELIAL FUNCTION TESTING

Endothelial function in fibromyalgia.

Date_____

Subjects ID#_____ control_____ pre_____ post_____

Age_____ Height_____ Weight _____

Last meal _____ Last medication _____

Room temperature _____

Rest: manual BP _____

20 min no recording (instrumentation)

Rest, file (-1) _____

1 min (resting forearm blood flow) peak blood flow_____ HR_____ BP_____

5 min (occlusion) cuff pressure_____ HR_____ BP_____

3 min (reactive hyperemia) peak blood flow_____ HR_____ BP_____

Resistance exercise session: comments_____

Post-exercise recovery, file (-2)_____

15-20 min (post exercise recovery) HR_____ BP_____

16-17 min (post exercise blood flow) peak blood flow____ _HR_____ BP_____

17-22 min (occlusion) cuff pressure_____HR_____ BP_____

22-25 min (reactive hyperemia) peak in blood flow____HR_____ BP_____

APPENDIX G: TENDER POINT ASSESSMENT

The Florida State University
Tender Point Assessment

Subject ID#_____
Date_____

	Tender	Point Sensitivity
Occiput……	_____	_____
At the suboccipital muscle insertions.		
Low cervical……	_____	_____
At the anterior aspects of the intertransverse spaces at C5-C7.		
Trapezius……	_____	_____
At the midpoint of the upper border.		
Supraspinatus……	_____	_____
At origins, above the scapula spine near the medial border.		
Second rib……	_____	_____
At the second costochondral junctions, just lateral to the junctions on upper surfaces.		
Lateral epicondyle……	_____	_____
At 2cm distal to the epicondyles.		
Gluteal……	_____	_____
At the outer quadrants of buttocks in anterior fold of muscle.		
Greater trochanter…….	_____	_____
At posterior to the trochanteric prominence.		
Knee……	_____	_____
At the medial fat pad proximal to the joint line		

APPENDIX H: ONE-REPETITION MAXIMAL STRENGTH TESTING

The Florida State University
Research on Strength Training and Fibromyalgia

Subject Number_____

Date_____

Chest Press 1-RM _____ Settings_____

Leg Press 1-RM _____ Settings_____

Leg Extension 1-RM _____ Settings_____

Seated Row 1-RM _____ Settings_____

Leg Curl 1-RM _____ Settings_____

Date_____

Chest Press 1-RM _____

Leg Press 1-RM _____

Leg Extension 1-RM _____

Seated Row 1-RM _____

Leg Curl 1-RM _____

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BIOGRAPHICAL SKETCH

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EDUCATION:

Florida State University, Tallahassee, FL

8/03-present Ph.D. candidate, Exercise Physiology
9/01-5/03 M.S., Exercise Physiology

The University of North Carolina at Greensboro, Greensboro, NC

9/94-5/99 B.S., Exercise and Sport Science

HONORS/AWARDS:

Student Research Award, Southeast Chapter of the American College of Sports Medicine, 2009.

University Graduate Student Research and Creativity Award, Florida State University, 2008.

American College of Sports Medicine Foundation Research Grant. *The effect of resistance training on pain, autonomic and endothelial function in women with fibromyalgia.* June 10, 2007-June 9, 2008.

Award for Best Presentation, Research and Creativity Day, College of Human Sciences, Florida State University, 2007.

Student Research Award, Southeast Chapter of the American College of Sports Medicine, 2004.

PUBLICATIONS:

Kingsley, J. D., Panton, L.B., McMillan, V., & Figueroa, A. (in press). Cardiovascular autonomic modulation after acute resistance exercise in women with fibromyalgia. *Archives of Physical Medicine and Rehabilitation.*

Panton, L. B., **Kingsley, J. D.**, St. John, N., McMillan, V., Mathis, R., Van Tassel, J., & Figueroa, A. (2009). Effects of resistance training and chiropractic treatment in women with fibromyalgia. *Complementary and Alternative Medicine, 15*, 321-328.

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Panton, L. B., Kushnick, M., **Kingsley, J. D.**, Moffatt, R., Haymes, E. M., & Toole, T. (2007). Pedometer measurement of physical activity and chronic disease risk factors of obese lower socioeconomic status African American women. *Journal of Physical Activity and Health, 4*, 447-458.

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Kingsley, J. D., Panton, L. B., Toole, T., Sirithienthad, P., Mathis, R., & McMillan, V. (2005). The effects of a 12 week strength-training program on strength and functionality in women with fibromyalgia. *Archives Physical Medicine Rehabilitation, 86*, 1713-1721.

RESEARCH PRESENTATIONS:

A. National

Kingsley, J. D., Panton, L. B., McMillan, V., & Figueroa, A. (2007) *Autonomic dysfunction at rest and during isometric exercise in women with fibromyalgia*. Poster presented at American College of Sports Medicine Convention, New Orleans, LA

Kingsley, J. D., Panton, L. B., Lee, J., McMillan, V., Fernhall, B., & Figueroa, A. (2006). *Exercise pressor response in overweight and obese women with fibromyalgia.* Poster presented at American College of Sports Medicine Convention, Denver, CO.

Kingsley, J. D., Panton, L. B., Toole, T., Moffatt, R., Kushnick, M., & Haymes, E. M. (2005). *Cardiovascular risk factors of low socioeconomic overweight and obese women following 12-month use of pedometers*. Paper presented at American College of Sports Medicine Convention, Nashville, TN.

Kingsley, J. D., Panton, L.B., Toole, T., Holton, E., Abboud, G., Sirthienthad, P., McMillan, V. (2003). *The comparison of functionality between older women and women diagnosed with fibromyalgia utilizing the Cs-PFP*. Paper presented at American College of Sports Medicine Convention, San Francisco, CA.

B. Regional

Kingsley, J.D., Panton, L.B., McMillan, V., Figueroa, A. (2009). *Forearm blood flow and vasodilatory capacity in women with fibromyalgia.* Poster presented at Southeast Chapter of the American College of Sports Medicine Convention, Birmingham, AL. **(Award Winner)**

Kingsley, J. D., Panton, L. B., Toole, T., Sirithienthad, P., Mathis, R., & McMillan, V. (2005). *The comparison of functionality between older adults, women diagnosed with fibromyalgia and healthy control women.* Paper presented at Southeast Chapter of the American College of Sports Medicine Convention, Charlotte, NC.

Kingsley, J. D., Panton, L. B., Toole, T., Sirithienthad, P., Mathis, R., & McMillan, V. (2005). *The comparison of functionality between older adults, women diagnosed with fibromyalgia and healthy control women.* Poster presented at Southeast Chapter of the American College of Sports Medicine Convention, Charlotte, NC.

Kingsley, J. D., Panton, L. B., Toole, T., Sirithienthad, P., Mathis, R., McMillan, V. (2004). *The effects of strength training in women with fibromyalgia.* Paper presented at Southeast Chapter of The American College of Sports Medicine Convention, Atlanta, GA. **(Award winner)**

Kingsley, J. D., Panton, L. B., Toole, T., Sirithienthad, P., Mathis, R., & McMillan, V. (2003). *Relationship between total myalgic score, fibromyalgia impact, and functionality in women with fibromyalgia.* Poster presented at Southeast Chapter of the American College of Sports Medicine Convention, Atlanta, GA.

PROFESSIONAL ASSOCIATIONS:

American Heart Association/American Stroke Association (member since 2006)
American Association for the Advancement of Science (member since 2005)
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Midwest Chapter – American College of Sports Medicine (member since 2009)
National Strength and Conditioning Association (member since 2002)