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Responses to Exercise Differ For Chronic Fatigue Syndrome Patients with Fibromyalgia

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Abstract

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) are chronic multisymptom illnesses with substantial clinical and diagnostic overlap. We have previously shown that when controlling for aerobic fitness and accounting for comorbid FM, CFS patients do not exhibit abnormal cardiorespiratory responses during maximal aerobic exercise compared to healthy controls, despite differences in pain and exertion.

Purpose—The purpose of the present study was to examine cardiac and perceptual responses to steady-state, submaximal exercise in CFS patients and healthy controls.

Methods—Twenty-one CFS patients [13 CFS with comorbid FM (CFS+FM)] and 14 controls completed 20 minutes of submaximal cycling exercise. Impedance cardiography was used to determine cardiac responses during exercise. Systolic blood pressure (SBP), perceived exertion (RPE) and leg-muscle pain were also measured. Data were analyzed using a doubly-multivariate, repeated-measures MANOVA to model the exercise response.

Results—There was a significant multivariate Time by Group interaction ($p < 0.05$). The CFS +FM group exhibited an exercise response characterized by higher stroke index, ventilatory equivalents for oxygen and carbon dioxide and RPE, lower SBP and similar HR responses.

Conclusions—The present results extend upon our previous work with maximal exercise and show that CFS and CFS+FM differ in their responses to steady-state exercise. These results highlight the importance of accounting for comorbid conditions when conducting CFS research, particularly when examining psychophysiological responses to exercise.

Keywords

pain; fatigue; impedance cardiography; stroke volume; perceived exertion

Introduction

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) are chronic multisymptom illnesses with substantial clinical and diagnostic overlap. The primary complaint of CFS patients, predictably, is debilitating fatigue while the primary complaint of FM patients is chronic widespread pain. The two conditions are highly comorbid up to 70% of CFS patients fulfill American College of Rheumatology (ACR) criteria for diagnosis of FM (4, 5, 15, 38).

Commonly, CFS patients report an exacerbation of their symptom complex as a result of even minimal exertion. Accordingly, acute exercise has been used as a stressor to determine whether abnormalities in cardiorespiratory and metabolic systems might underlie the patients' poor exercise tolerance and worsening of symptoms following exercise. Results from these studies have been equivocal (2, 8, 10, 20). Our previous work highlighted the importance of controlling for aerobic fitness and accounting for FM status on cardiorespiratory and perceptual responses to exercise in CFS (8). In that work, initial analysis of the data indicated that CFS patients had lower cardiorespiratory responses and enhanced exertion and pain responses to maximal exercise compared to healthy, sedentary controls; data that appeared consistent with prior work (20, 29). However, when the data were analyzed while controlling for aerobic fitness and accounting for the presence of comorbid FM (CFS+FM), group differences for cardiorespiratory responses were eliminated and the only remaining differences between the groups was that the CFS+FM group reported greater exertion and pain during exercise compared to healthy control subjects (8). Our results suggested that the equivocal findings of previous CFS research were likely due to a failure to effectively control for differences in aerobic capacity between patients and controls and/or to account for comorbid illness.

Maximal exercise testing has provided important insights into the aerobic capacities and cardiorespiratory systems of patients (8, 35, 36). This type of protocol is important for determining cardiorespiratory responses that occur during high intensity exercise and provides critical information concerning metabolic adjustments that occur at or above the ventilatory threshold. However, there are limitations inherent to employing maximal exercise protocols such that steady-state, submaximal exercise could provide a better option for determining cardiorespiratory responses in CFS populations. First, maximal efforts are almost certainly not encountered under normal circumstances. Thus, maximal exercise tests have limited generalizability to daily life. Second, time to volitional exhaustion for maximal exercise tests can have substantial variability making direct comparisons between individuals and groups difficult. Steady-state submaximal protocols can be designed to deliver relative exercise intensities for a standardized period of time. Third, ramped tests that are often used in maximal exercise protocols, force the cardiorespiratory system to constantly adapt to a progressively increasing workload and may mask abnormal adaptations and/or responses that may be revealed during submaximal and steady-state exercise. Fourth, maximal exercise tests make it difficult to obtain additional physiological information beyond heart rate, blood pressure, oxygen consumption and carbon dioxide production. Exercise tests conducted at lower intensities provide the opportunity to use methods such as noninvasive impedance cardiography to obtain potentially important hemodynamic information about the cardiac cycle.

The purpose of the present investigation was to contrast the cardiorespiratory and perceptual responses to submaximal exercise of CFS patients with and without comorbid FM to those of sedentary healthy controls. Our 2006 study (8) highlighted the importance of aerobic fitness and FM status in interpreting exercise-testing results. In the current study, we accounted for FM status (CFS+FM) and exercised individuals at a relative (40% of peak aerobic capacity) intensity to account for varying fitness levels. The purpose of the present

investigation was to contrast the cardiorespiratory and perceptual responses to submaximal exercise of CFS patients with and without comorbid FM to those of sedentary healthy controls.

Methods

Subjects

Data for the present investigation were collected as part of a larger study intended to determine the influence of exercise on cognitive function in CFS (8). Sixty-five participants were randomly assigned to either an exercise or no exercise/quiet rest condition. Data reported here are for those participants assigned to the exercise condition. Thirty-five participants completed the submaximal exercise protocol [$n=21$ CFS ($n=8$ CFS Only, $n=13$ CFS+FM); $n=14$ Healthy Control]. Participants with CFS were recruited from a large patient pool available through the New Jersey CFS Cooperative Research Center. All CFS patients met the 1994 Center for Disease Control case definition of CFS and had no known medical or psychiatric causes for their symptoms (12). Patients with comorbid FM were diagnosed based on the ACR 1990 criteria for fibromyalgia (38). Sedentary healthy control subjects were also recruited from a control subject pool at the New Jersey CFS Cooperative Research Center. These individuals reported themselves to be in “good” or “excellent” health and taking no medications other than birth control pills. “Sedentary” was defined as working in an occupation that did not require moderate-to-intense physical labor and not participating in physical exercise (leisure time or sport conditioning) for more than one session per week.

Exclusion criteria for all CFS patients were based on the clinical criteria listed in the Centers for Disease Control case definition (12). Sedentary controls were excluded if they had a history of cardiovascular, respiratory, neurological, or major psychiatric disorders or were taking any medications other than oral contraceptives. The study was approved by the Institutional review boards of the Veterans Affairs Medical Center (VAMC), East Orange, NJ and the University of Medicine and Dentistry – New Jersey Medical School, Newark, NJ. Written informed consent was obtained for all participants in the study.

Experimental Procedures

The study was performed under controlled environmental conditions (20–24°C and 40–60% relative humidity) between 11am and 2pm. A maximal exercise test, performed as part of a separate study (8) approximately 2 weeks earlier, was used to determine the submaximal exercise intensities for the present study. Maximal exercise testing entailed a ramped cycle-ergometry protocol performed to volitional exhaustion to determine individual peak oxygen consumption (VO_{2peak}) values. A maximal effort was determined based on meeting at least two of the following criteria: 1) respiratory exchange ratio >1.1 , 2) change in $VO_2 < 200$ ml with an increase in work, 3) rating of perceived exertion (RPE) of 17 or greater and 4) achieving 85% of age predicted maximal heart rate. For the present protocol, subjects reported to the Human Performance Laboratory located at the East Orange VAMC having abstained from smoking for 2 hours, ingesting caffeine and alcohol for 4 hours, and exercising for 24 hours prior to testing. Participants were also instructed to fast for the 4 hours preceding their exercise test. After signing the informed consent, subjects completed the profile of mood states (POMS) and the short-form McGill Pain Questionnaire (MPQ) in order to assess mood and resting pain, respectively, prior to exercise (27, 28).

Instrumentation

A modified lead II ECG was used to monitor cardiac activity throughout the test. Blood pressure was measured during the last 30 seconds of every 4-minute interval during exercise

using a Dinamap (Model 1846 SX, Critikon, Tampa, FL) automated blood pressure unit. Expired air was collected breath-by-breath (i.e. O₂ consumption, CO₂ production, and ventilation) using a two-way nonrebreathing valve (Hans-Rudolph, Kansas City, MO) and was analyzed with the Max-1 metabolic measurement system (Physio-Dyne Instruments, Quoge, NY). The system was calibrated before each test using standard gases with known concentrations and a standard 3-liter syringe.

An impedance cardiograph (University of Miami, Model R03) was used to obtain noninvasive measures of stroke volume (SV), cardiac output (Q), preejection period (PEP) and left ventricular ejection time (LVET). A tetrapolar aluminum band electrode configuration was employed as previously described (33). Stroke index (SI) was derived by dividing SV by body surface area [$\text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} / 139.2$] and cardiac index (CI) was derived by dividing Q by body surface area. Total peripheral resistance (TPR) was calculated as mean arterial pressure divided by the ratio Q/16.67 (16). An indexed value of TPR (TPRI) was calculated as mean arterial pressure divided by the ratio CI/16.67. The Heather Index (HI; ohms/second²) was used as an estimate of myocardial contractility (17). Impedance cardiographic data were collected during the final 30 seconds of each 2-minute interval during exercise. Data were ensemble averaged and scored as previously described (31).

Exercise Testing

Subjects were seated on an electronically-braked cycle ergometer (Sensormedics, Loma Linda, CA), with the seat and handlebars adjusted for optimal performance, and allowed a few minutes to habituate to the cycle and various monitoring devices. The exercise test began with a 1-minute warm-up at 20 watts. Exercise intensity was then increased to a level designed to elicit a metabolic response equal to 40% of each participant's VO_{2peak}. Exercise intensity was maintained by adjusting the power output of the cycle ergometer. Adjustments were made when the oxygen consumption equivalent to the target percentage of VO_{2peak} varied by ± 3 milliliters per kilogram body weight of the desired value. Subjects were instructed to maintain a pedaling cadence between 60–70 rpm that was signaled by the digital readout mounted on the cycle ergometer. Subjects exercised for 20 minutes followed by a gradual 5-minute active recovery.

Ratings of perceived exertion (RPE) were obtained during the last 10 seconds of every minute during the submaximal exercise test and every 30 seconds during recovery using the Borg 6–20 category scale (3). Before exercise, subjects were given standard instructions as to the proper use of the Borg 6–20 category scale. Briefly, subjects were instructed that the Borg 6–20 scale would be used to determine the intensity of effort or stress felt only in the legs during exercise and recovery. Subjects were further instructed that each number represents a category of sensation which is ordered according to its intensity and that the verbal anchors (e.g. “very light,” “light,” “somewhat hard,” “hard,” etc.) should be used to help determine the level of effort at the moment they are asked to rate. Subjects were also provided cognitive anchors at the high and low ends of the perceptual continuum. Specifically, subjects were instructed that a “6” on the scale refers to the amount of effort exerted in their legs while they were sitting in a chair (i.e. no effort), while a “20” refers to the most effort imaginable (e.g. carrying a child out of a burning building or finishing a marathon).

Leg muscle pain intensity ratings were obtained during the last 10 seconds of every minute during exercise and every 30 seconds during recovery. Pain intensity was measured by use of a validated category-ratio pain intensity scale (9). The pain intensity scale ranges from 0 (“no pain at all”) to 10 (“extremely intense pain, almost unbearable”). Subjects were instructed that the 0–10 pain intensity scale would be used to determine the intensity of pain

felt only in the leg muscles during exercise and recovery. Subjects were further instructed that: 1) pain is defined as the intensity of hurt felt in the leg muscles; 2) each number represents a category of sensation that is ordered according to its intensity; and 3) the verbal anchors (e.g. “no pain,” “weak pain,” “moderate pain,” “strong pain,” “extremely intense pain,” etc.) should be used to help determine the level of pain intensity at the moment they are asked to rate.

Statistical Analyses

For the purpose of this investigation, the cardiovascular and perceptual variables collected during exercise were of primary interest. Given the large number of potential variables which could be derived from the impedance cardiographic data and the fact that many of these variables are directly related to one another, we selected two relevant yet theoretically independent variables, heart rate (HR) and stroke index (SI). In order to best capture the cardiovascular and perceptual response to the submaximal exercise we also included systolic blood pressure (SBP) and RPE in our model. Although ratings of leg muscle pain were also collected during exercise, RPE was chosen to be in the model because of its established relationship to cardiovascular responses to exercise. We chose these variables deliberately in order to evaluate multiple aspects of the cardiovascular response to exercise in these patients, while at the same time limiting redundancy between variables. As a test of the primary hypothesis, the selected variables were analyzed using a Group by Time (3×6) doubly-multivariate, repeated-measures MANOVA with an overall level of significance (α) equal to 0.05. The overall MANOVA compared the groups on a linear combination of all four dependent variables across the repeated-measures collected during the exercise bout. A total sample of 33 participants provided a power ($1-\beta$ error probability) of .929 for the overall MANOVA, given an effect size [$f^2(V)$] of .36 and $\alpha = 0.05$. For the purpose of more fully characterizing the response to exercise and exploring possible relationships to other variables, averages of the remaining participant characteristic, cardiorespiratory, impedance cardiographic and perceptual variables were compared with a series of exploratory one-way ANOVAs with group membership as the lone factor and $\alpha = 0.05$. These comparisons were based on data collected during minutes four through twenty of the submaximal exercise protocol, to reflect steady-state. Effect sizes for these comparisons were calculated using Cohen's d (6).

Results

Of the original 35 participants, two individuals, a CFS patient with comorbid fibromyalgia and a healthy control, were excluded from analysis due to incomplete impedance cardiography data. Characteristics, baseline mood and symptoms for the final sample ($N=33$) are detailed in Table 1. The participant groups [CFS Only ($n = 8$); CFS+FM ($n = 12$); controls ($n = 13$)] did not differ significantly in regards to age, height, weight, resting heart rate, resting systolic and diastolic blood pressure, reported leisure-time physical activity, or VO_{2peak} . The groups were also similar in regards to sex breakdown, and level of education. Both CFS patient groups reported significantly greater fatigue, confusion, and overall mood disturbance and less vigor than controls ($p < 0.05$; POMS). Current pain intensity, documented immediately prior to exercise using the MPQ, was greater for the CFS+FM group compared to both the CFS Only group and controls ($p < 0.05$).

Baseline Cardiac & Submaximal Exercise

There were no significant group differences in baseline measures of HR, SI, CI, PEP, LVET, TPRI or HI ($p > 0.05$; See Table 1). The doubly multivariate repeated-measures comparison of the physiological and perceptual variables collected during exercise resulted in a significant multivariate Group by Time interaction (Wilks' $\Lambda = 0.046$; $F_{(40, 22)} = 2.006$; $p <$

0.05). This interaction effect shows that the combined changes in the dependent variables observed during exercise differed as a function of group. Inspection of these data (see Figure 1) indicates that the CFS+FM group exhibited an exercise response characterized by higher RPE and SI and lower SBP relative to the other groups. No differences in heart rate during exercise were apparent. The significant interaction was eliminated when a similar analysis of the same variables was conducted with the CFS Only and CFS+FM patients collapsed into one group, demonstrating that the CFS Only and CFS+FM groups had different cardiac and perceptual responses to submaximal exercise.

Average cardiovascular and perceptual responses collected during submaximal exercise (minutes 4–20) are listed in Table 2. The groups did not significantly differ on either percent oxygen consumption or average Watts during exercise, however the effect size difference for Watts between the CFS+FM and CFS only groups was large. CFS+FM patients had higher ventilatory equivalents for O₂ and CO₂ and reported greater leg muscle pain (see Figure 2) during exercise compared to both CFS Only patients and controls. In addition, individuals in the CFS+FM group had lower SBP and higher RPE compared to controls. Impedance cardiography data during exercise are listed in Table 3. CFS+FM patients had significantly higher SI compared to both CFS Only and controls. The CFS+FM group had moderately, but nonsignificantly, lower TPRI and higher CI than both CFS Only and control groups (See Figure 3).

Discussion

Our previous work using maximal exercise testing found no differences in the cardiorespiratory responses between CFS patients and healthy controls when matched on aerobic fitness (8). These results challenged earlier studies reporting slow acceleration of heart rate and low ventilatory responses in CFS suggestive of subtle cardiac abnormalities or autonomic dysfunction (20, 29). In the present investigation, we sought to extend upon our previous research by determining the cardiorespiratory and perceptual responses to moderate intensity, steady-state exercise in CFS. Our results indicate that CFS patients with comorbid fibromyalgia differ in their response to exercise compared to CFS patients without comorbid FM and healthy sedentary controls. These differences were characterized by an elevated perception of exertion, an exaggerated stroke index response, and a diminished systolic blood pressure response. The CFS+FM patients also had moderately lower total peripheral resistance and experienced greater musculoskeletal pain during submaximal exercise.

The elevated stroke index response in the CFS+FM patients was unexpected. In general stroke volume is determined by five primary factors: 1) the volume of blood returned to the heart by the venous system, 2) the ventricular capacity or compliance of the heart (i.e. Frank Starling mechanism), 3) ventricular contractility, 4) arterial pressure placed against the ventricles, and 5) systemic vascular resistance. Examination of the data shows no differences in baseline variables including systemic vascular resistance, stroke index and cardiac index. This suggests that differences in blood volume, which have been previously observed (19) and hypothesized to contribute to stroke volume abnormalities in this population (32), are an unlikely explanation for the observed results. However, when exposed to an exercise challenge several interesting findings emerged. The elevated SI response to submaximal exercise in the CFS+FM patients was accompanied by a significantly lower SBP response and a trend towards lower diastolic blood pressure, lower total peripheral resistance and higher cardiac contractility. When examined in aggregate, these results point towards a cardiovascular system that is relatively normal at rest (baseline) but that does not show the expected increase in systolic blood pressure in response to a light exercise challenge.

For the CFS+FM patients, stroke volume may have increased to a greater extent in order to maintain blood pressure and oxygen delivery to active skeletal muscle during exercise. The mechanism for this is not apparent, but recent research in CFS suggests that muscle bioenergetic abnormalities, expressed as abnormal phosphocreatine to adenosine triphosphate ratios and reduced proton efflux rates, are present in a subset of CFS patients (18). These reported abnormalities were associated with greater cardiac contractility during standing and interpreted as enhanced cardiac work during a relative physical stressor. In addition, work by McCully and colleagues (25, 26) have demonstrated abnormal muscle metabolism, reduced oxygen delivery and slower recovery of oxygen saturation after exercise in CFS patients compared to controls. These results suggest impaired vascular control in CFS that could compromise muscle blood flow and metabolism during exercise. An enhanced stroke index response could be indicative of compensation to maintain muscle blood flow and oxidative metabolism during exercise. The elevated ventilatory equivalents for oxygen and carbon dioxide (indices of ventilatory efficiency) also indicate that the CFS +FM patients were less efficient, requiring greater ventilation to remove excess carbon dioxide accumulation during low intensity exercise, perhaps to maintain oxygen delivery to working muscle. It is important to note that none of the studies cited above accounted for FM status of CFS patients. Our results suggest this explanation would only apply to CFS patients with comorbid FM.

Our results add to the growing literature suggesting autonomic nervous system (ANS) dysfunction in CFS (13, 30) and FM (14, 21, 23). Previous investigations of the hemodynamic and metabolic responses to exercise suggested that patients with CFS might exhibit abnormalities indicative of dysfunction of the central cardiovascular control center. The present study suggests the cardiovascular responses of CFS patients without comorbid FM are similar to healthy control subjects. However, patients with concurrent diagnoses of CFS and FM exhibit abnormal responses. Further, FM patients have been shown to have low baroreflex sensitivity (BRS) that was not improved with resistance exercise training (11). Our observed trend of lower peripheral resistance as well as significantly lower SBP in patients with CFS+FM during mild exercise suggests that autonomic control of vasoconstriction to regions during exercise may be compromised perhaps due in part to low BRS. This would be consistent with converging evidence of normal ANS or enhanced sympathetic activity at rest and impaired modulation of the ANS response to a variety of experimental stressors in FM (34). In general, FM patients have been shown to exhibit a hypoactive ANS, both in general (1) and in response to exercise. As pointed out by Adler and Geenen (1), a major limitation of previous research of ANS function in FM is the failure to control for physical activity and/or fitness, variables that have a profound influence on the ANS.

Under normal circumstances, during exercise and in response to the subsequent impact of vasodilation on blood pressure, peripheral baroreceptors are stimulated and activate brain regions responsible for cardiovascular control (central command). This resultant efferent signaling elevates sympathetic activity, causing reflexive vasoconstriction, increased HR, myocardial contractility and/or stroke volume. The elevated stroke index exhibited by the CFS+FM group could be interpreted as evidence that autonomic regulation was at least partially intact. However, HR was not similarly affected, and this overall response did not reverse the abnormal blood pressure and peripheral resistance trends observed during exercise. The integrated result was an abnormal physiological response to a gentle exercise demand for the CFS+FM group. This finding encourages continued attention to the constitution of the patient group under study.

In addition to the cardiovascular differences, CFS+FM patients also experienced greater pain and exertion during submaximal exercise, despite exercising at a lower absolute

workload. These data are consistent with our prior work using maximal exercise testing procedures and extend them to steady-state and longer duration submaximal exercise (7, 8). CFS patients without comorbid fibromyalgia did not report greater pain or exertion during submaximal exercise, challenging the widespread assumption that CFS patients have altered effort sense or that CFS is an illness of altered effort sense (24, 37). Our results suggest that chronic widespread pain can influence perceived exertion during exercise perhaps through enhanced sensory input from contracting skeletal muscle during exercise.

Our data indirectly contradict previous research showing reduced stroke volume in CFS. Peckerman and colleagues (32), using impedance cardiography, reported reduced stroke volume at rest in CFS patients categorized as severe compared to both a less severe CFS group and sedentary health controls. Similarly, Hurwitz and colleagues (19) reported moderately reduced stroke volume at rest in CFS that was almost entirely explained by low blood volume. A major strength of the Hurwitz (19) study was the categorization of controls as either sedentary or active and the assessment of fitness in the CFS and sedentary control groups. We did not observe differences in any of resting measures, including SI, between patients and controls (see Table 1), although our small sample sizes may have precluded detection.

Limitations

The primary limitation of the present study is the small sample size, particularly the size of the CFS Only group (n=8). Despite the small sample we did observe a significant interaction for the overall model which speaks to the power of the finding. However, a larger sample would permit us the freedom to include additional variables in the model as well as the possibility of planned comparisons to explore the group differences between individual variables of interest. Related to that point, our decision to evaluate a single *a priori* defined model of cardiovascular and perceptual variables using the MANOVA has limited our ability to make conclusions about how CFS patients with and without comorbid FM, as well as healthy controls, may differ in regards to influence of submaximal exercise on individual variables.

Another limitation is related to intensity of the submaximal exercise employed in the present investigation. As was pointed out in the Introduction, the use of a submaximal exercise protocol enabled us to use noninvasive impedance cardiography to monitor the hemodynamics of the cardiac cycle during exercise. However, only a single relative intensity (40% $\text{VO}_{2\text{peak}}$) of submaximal exercise was employed in our study. We cannot rule out possibility that the pattern of cardiovascular and perceptual variables for CFS patient groups and controls during exercise may be different from our results at greater or lower intensities. It is also worth noting that, despite a lack of significant difference between groups in regards to level of fitness and the fact that all groups exercised at roughly the same relative intensity of exercise, the CFS+FM group on average exercised at a relatively low absolute intensity (25 W) compared to that in the CFS only group (46 W). Given this fact, it may be that we have underestimated the magnitude of the differences in cardiovascular and perceptual responses between CFS patients with comorbid FM and pure CFS patients and healthy controls. Finally, the design of the current study is limited in that it does not permit us to draw conclusions as to whether the differential response of CFS+FM patients to submaximal exercise is due simply to the presence of FM or the combination of CFS and FM.

Conclusions

Using a submaximal exercise challenge and employing a multivariate model to determine the cardiovascular and perceptual responses to steady-state exercise, we found that CFS patients with comorbid FM differ from CFS patients without widespread pain. These differences were characterized by exaggerated stroke index, low pressure, and elevated exertion and pain. When CFS and CFS+FM patients were combined in the model, the differences were eliminated, underscoring the necessity of controlling for FM in CFS research. The pattern of observed responses in the CFS+FM patients suggest autonomic nervous system dysfunction that may lead to chronic blood flow abnormalities and that clearly could be implicated in the sequelae of illnesses associated with unexplained fatigue and pain.

FM is the most common comorbid illness in CFS. This has led some to speculate that these and other multisymptom illnesses represent a spectrum of functional somatic disorders (22), perhaps reflecting common pathophysiological mechanisms. However, beyond symptom profiles, CFS and FM have rarely been directly compared. Our results suggest that having both CFS and FM is different from having CFS without FM. This in some ways challenges the spectrum hypothesis that CFS and FM have the same underlying pathophysiology. Future research with larger samples of patients and the inclusion of an FM group without comorbid CFS would help to further clarify similarities and differences in these complex illnesses.

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Figure 1.

Individual plots for each of the dependent variables included in the MANOVA; Values on the horizontal axes represent the duration of submaximal exercise in minutes. Abbreviations: CFS Only (chronic fatigue syndrome patients without comorbid fibromyalgia), CFS+FM (chronic fatigue syndrome patients with comorbid fibromyalgia), CO (healthy controls).

Figure 2.

Plot of leg muscle pain ratings during exercise for each group; Values on the horizontal axes represent the duration of submaximal exercise in minutes. Abbreviations: CFS Only (chronic fatigue syndrome patients without comorbid fibromyalgia), CFS+FM (chronic fatigue syndrome patients with comorbid fibromyalgia), CO (healthy controls).

Figure 3.

Plots of CI and TPRI during exercise for each group; Values on the horizontal axes represent the duration of submaximal exercise in minutes.

Abbreviations: CFS Only (chronic fatigue syndrome patients without comorbid fibromyalgia), CFS+FM (chronic fatigue syndrome patients with comorbid fibromyalgia), CO (healthy controls).

Table 1Participant characteristics, baseline mood and symptoms, Mean ($\pm$ SD).

	CFS Only (n=8)	CFS+FM (n=12)	Controls (n=13)
Age (yr)	37.3 ($\pm$ 9.6)	39.8($\pm$ 8.8)	35.2 ($\pm$ 11.1)
Height (cm)	171 ($\pm$ 11.4)	162.8($\pm$ 9.5)	163.9 ($\pm$ 10.7)
Weight (kg)	74.2 ($\pm$ 10.7)	63.1($\pm$ 15)	68.7 ($\pm$ 19.1)
Resting HR (bpm)	73.5 ($\pm$ 11.9)	80.1($\pm$ 12.7)	69.9 ($\pm$ 11.0)
Resting SBP (mmHg)	119.8 ($\pm$ 11.2)	109.7($\pm$ 13.5)	113.3 ($\pm$ 14.2)
Resting DBP (mmHg)	79.3 ($\pm$ 8.4)	72.9($\pm$ 6.6)	71.8 ($\pm$ 7.3)
Leisure-time PA (METs/wk)	19.4 ($\pm$ 17.7)	20.3($\pm$ 25.7)	22.0 ($\pm$ 17.4)
VO_{2peak} (ml/kg/min)	26.2 ($\pm$ 9.0)	24.2($\pm$ 5.4)	30.3 ($\pm$ 8.1)
Cardiac Index (l/min/m ²)	6.0 ($\pm$ 2.4)	8.4 ($\pm$ 3.9)	6.5 ($\pm$ 2.8)
TPRI (mmHg·m ² /min/l)	16.1 ($\pm$ 6.1)	11.5 ($\pm$ 5.6)	17.3 ($\pm$ 12.6)
Stroke Index (ml/beat/m ²)	18.3 ($\pm$ 7.5)	26.8 ($\pm$ 12.8)	22.9 ($\pm$ 8.9)
Heather Index (Ohms/s ²)	1.98 ($\pm$ 0.53)	2.21 ($\pm$ 0.71)	1.85 ($\pm$ 0.59)
Preejection Period (ms)	121.1 ($\pm$ 8.5)	112.5 ($\pm$ 17.4)	122.1 ($\pm$ 19.4)
LVET (ms)	269.6 ($\pm$ 38.6)	251.6 ($\pm$ 32.6)	264.1 ($\pm$ 29)
Education (yr)	17.4($\pm$ 1.8)	17.2($\pm$ 2.7)	17.8($\pm$ 2.2)
Sex (% Female)	62.5	83.3	69.2
Tension (POMS)	10.9($\pm$ 10.9)	9.0($\pm$ 5.7)	4.1($\pm$ 2)
Depression (POMS)	9.3($\pm$ 11.4)	5.8($\pm$ 5.0)	2.4($\pm$ 1.9)
Anger (POMS)	4.4($\pm$ 7.2)	2.3($\pm$ 1.9)	2.6($\pm$ 2.5)
Vigor (POMS)	12.8($\pm$ 8) ^a	8.1($\pm$ 6.0) ^a	20.9($\pm$ 4.7)
Fatigue (POMS)	14.5($\pm$ 5.9) ^a	17.8($\pm$ 5.8) ^a	2.7($\pm$ 1.5)
Confusion (POMS)	9.4($\pm$ 6.1) ^a	8.9($\pm$ 3.9) ^a	3.2($\pm$ 1.8)
TMD (POMS)	135.6($\pm$ 44.5) ^a	135.8($\pm$ 19.7) ^a	94($\pm$ 6.0)
MPQ Total	1.6($\pm$ 2.1)	6.0($\pm$ 5.6) ^{ab}	0.1($\pm$ 0.3)

Abbreviations: HR (heart rate); bpm (beats/min); SBP (systolic blood pressure); DBP (diastolic blood pressure); PA (physical activity); METs (metabolic equivalents); VO_{2peak} (peak aerobic capacity); LVET (left ventricular ejection time); TPRI (total peripheral resistance indexes by body surface area); POMS (Profile of Mood States); TMD (Total Mood Disturbance); MPQ (McGill Pain Questionnaire)

^aSignificantly different from Control ($p < 0.05$)

^bSignificantly different from CFS Only ($p < 0.05$)

Table 2

Group differences in response to submaximal exercise bout, Mean ($\pm$ SD).

	CFS Only (n=8)	CFS+FM (n=12)	Control (n=13)	Effect size (d) for CFS+FM – CFS Only	Effect size (d) for CFS+FM – Controls
% peak VO ₂	45.7 ($\pm$ 7.0)	52.9 ($\pm$ 16.9)	44.2 ($\pm$ 4.9)	0.54	0.75
VO ₂ (ml)	873 ($\pm$ 290)	781 ($\pm$ 302)	907 ($\pm$ 330)	-0.33	-0.42
VCO ₂ (ml)	790 ($\pm$ 296)	675 ($\pm$ 305)	762 ($\pm$ 282)	-0.40	-0.31
RER	0.89 ($\pm$ 0.06)	0.85 ($\pm$ 0.06)	0.84 ($\pm$ 0.05)	-0.76	0.24
VE (l/min)	23.4 ($\pm$ 7.8)	24.1 ($\pm$ 7.6)	24.4 ($\pm$ 6.9)	0.09	-0.04
RR (breaths/min)	20.9 ($\pm$ 4.0)	21.9 ($\pm$ 5.2)	24.1 ($\pm$ 3.0)	0.22	-0.54
VE/VO ₂	27.6 ($\pm$ 2.6)	31.4 ($\pm$ 2.9) ^b	27.8 ($\pm$ 3.4)	1.43	1.21
VE/VCO ₂	31.1 ($\pm$ 4.0)	37.1 ($\pm$ 4.9) ^b	33.1 ($\pm$ 4.0)	1.40	0.94
HR (beats/min)	100.9 ($\pm$ 9.6)	104.3 ($\pm$ 13.3)	105.5 ($\pm$ 18.6)	0.30	-0.08
SBP (mmHg)	134.7 ($\pm$ 16.6)	118.1 ($\pm$ 11.2) ^a	140.5 ($\pm$ 26.8)	-1.29	-1.12
DBP (mmHg)	74.7 ($\pm$ 8.0)	70.5 ($\pm$ 3.9)	77.5 ($\pm$ 9.8)	-0.75	-0.96
Watts	45.6 ($\pm$ 29.1)	25.0 ($\pm$ 9.8)	41.2 ($\pm$ 26.9)	-1.10	-0.61
RPE (6–20 scale)	10.6 ($\pm$ 1.6)	12.2 ($\pm$ 2.7) ^a	9.0 ($\pm$ 1.9)	0.71	1.42
Pain (0–10 scale)	1.3 ($\pm$ 1.3)	2.9 ($\pm$ 2.1) ^b	0.8 ($\pm$ 0.8)	0.93	1.39

Mean values are for data collected during minutes 4–20 of the submaximal exercise test. This timing was chosen to represent the steady-state portion of the test (40% VO_{2peak}). Effect sizes are reported as Cohen's *d* for differences between CFS+FM and CFS Only as well as differences between CFS+FM and controls. Abbreviations: SBP (systolic blood pressure), DBP (diastolic blood pressure)

^aSignificantly different from Control ($p < 0.05$)

^bSignificantly different from CFS Only and Control ($p < 0.05$)

Table 3

Averages for impedance cardiography data during exercise, Mean ($\pm$ SD).

	CFS Only (n=8)	CFS+FM (n=12)	Controls (n=13)	Effect size (<i>d</i>) for CFS+FM – CFS Only	Effect size (<i>d</i>) for CFS+FM – Controls
CI (l/min/m ²)	8.0 ($\pm$ 2.7)	12.4 ($\pm$ 4.2)	10.4 ($\pm$ 4.1)	1.25	0.5
TPRI (mmHg/min/l/m ²)	13.4 ($\pm$ 4.3)	8.8 ($\pm$ 5.2)	12.1 ($\pm$ 8.1)	-1.01	-0.51
SI (ml/beat/m ²)	21.8 ($\pm$ 6.7)	41.8 ($\pm$ 19.5) ^a	28.6 ($\pm$ 14.1)	1.33	0.81
HI (Ohms/s ²)	2.22 ($\pm$ 0.61)	2.58 ($\pm$ 0.65)	2.19 ($\pm$ 0.7)	0.59	0.59
PEP (ms)	96.3 ($\pm$ 12.5)	86.6 ($\pm$ 17.9)	78.7 ($\pm$ 20.3)	-0.64	0.43
LVET (ms)	227.5 ($\pm$ 21.6)	229.8 ($\pm$ 29.1)	234.8 ($\pm$ 34.6)	0.09	-0.16

Mean values are for data collected during minutes 4–20 of the submaximal exercise test. This timing was chosen to represent the steady-state portion of the test (40% VO_{2peak}). Effect sizes are reported as Cohen's *d*. Abbreviations: CI (cardiac index), TPRI (total peripheral resistance indexed by body surface area), HR (heart rate), SI (stroke index), HI (Heather index), PEP (pre-ejection period), LVET (left ventricular ejection time).

^aSignificantly different from CFS Only and Control ($p < 0.05$)