

Subclassifying Chronic Fatigue Syndrome through Exercise Testing

J. MARK VANNESS¹, CHRISTOPHER R. SNELL¹, DAVID R. STRAYER³,
LINE DEMPSEY IV², and STACI R. STEVENS²

¹University of the Pacific, Department of Sport Sciences, Stockton, CA; ²The Workwell Foundation, Ripon, CA; and ³Hemispherx Biopharma, Inc., Philadelphia, PA

ABSTRACT

VANNESS, J. M., C. R. SNELL, D. R. STRAYER, L. DEMPSEY IV, and S. R. STEVENS. Subclassifying Chronic Fatigue Syndrome through Exercise Testing. *Med. Sci. Sports Exerc.*, Vol. 35, No. 6, pp. 908–913, 2003. **Purpose:** The purpose of this study was to examine physiological responses of persons with chronic fatigue syndrome (CFS) to a graded exercise test. **Methods:** Cardiopulmonary exercise tests were performed on 189 patients diagnosed with CFS. Based on values for peak oxygen consumption, patients were assigned to one of four impairment categories (none, mild, moderate, and severe), using American Medical Association (AMA) guidelines. A one-way MANOVA was used to determine differences between impairment categories for the dependent variables of age, body mass index, percentage of predicted $\dot{V}O_2$, resting and peak heart rates, resting and peak systolic blood pressure, respiratory quotient (RQ), and rating of perceived exertion. **Results:** Significant differences were found between each impairment level for percentage of predicted $\dot{V}O_2$ and peak heart rate. Peak systolic blood pressure values for the “moderate,” and “severe” groups differed significantly from each other and both other groups. The more impaired groups had lower values. The no impairment group had a significantly higher peak RQ than each of the other impairment levels (all $P < 0.001$). Peak $\dot{V}O_2$ values were less than predicted for all groups. Compared with the males, the women achieved actual values for peak $\dot{V}O_2$ that were closer to their predicted values. **Conclusion:** Despite a common diagnosis, the functional capacity of CFS patients varies greatly. Stratifying patients by function allows for a more meaningful interpretation of the responses to exercise and may enable differential diagnosis between subsets of CFS patients. **Key Words:** GRADED EXERCISE, CARDIOPULMONARY ANALYSIS, FUNCTIONAL CAPACITY, PHYSICAL IMPAIRMENT, CARDIAC RESPONSE, FUNCTIONAL IMPAIRMENT, DIFFERENTIAL DIAGNOSIS

Chronic fatigue syndrome (CFS) is a complex illness characterized by pervasive fatigue, sleep disturbance, neurocognitive problems, joint and muscle pain, and numerous other symptoms. Researchers from DePaul University have estimated that as many as 836,000 Americans may be afflicted with CFS, with approximately 90% of patients yet to be diagnosed and provided appropriate treatments. Although CFS seems to afflict both males and females of various ethnic backgrounds from childhood to adulthood, the syndrome is most commonly diagnosed in females (18). However, this may be in part a function of women visiting doctors more often overall. In the population as a whole, CFS is probably just as prevalent among

men (10). The corresponding economic impact resulting from the disability caused by CFS is becoming an important societal concern (24). Because CFS is an emerging illness, there are few guidelines for the evaluation of patients.

In 1988, the U.S. Centers for Disease Control and Prevention (CDC) established a case definition for CFS to assist clinicians and researchers in diagnosing patients in a more uniform manner (16). The CDC revised the case definition for CFS in 1994 (12). For a diagnosis to be made, any medical conditions that may explain the presence of fatigue must be ruled out. The fatigue associated with the syndrome is described as debilitating or easy fatigability in a person who has no previous history of similar symptoms, that does not resolve with bedrest, and that is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level for a period of at least 6 months (16). Fukuda et al. (12) defines the fatigue inherent in CFS as clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities. Additionally, an individual must exhibit four or more of the following symptoms; sore throat;

Address for correspondence: J. Mark VanNess, Department of Sport Sciences, University of the Pacific, Stockton, CA 95211; E-mail: mvanness@uop.edu.

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tender cervical or axial lymph nodes; muscle pain; multi-joint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep and post-exertional malaise lasting more than 24 h.

The current diagnostic criteria for CFS (12) focus primarily on the subjective symptoms associated with the illness. Consequently, the etiology, pathophysiology, and pathogenesis of the disease are still not clearly understood (25). Researchers have documented immune (20) and central nervous system dysfunction (28) as well as metabolic (25–27) and endocrine (18) abnormalities in CFS patients. Although some progress has been made toward identifying a common cause underlying the symptoms of CFS (9), currently no single diagnostic test exists. The continued reliance on consensus of clinical description in the absence of measurable pathology has resulted in a heterogeneous patient population and inconsistency among research findings (35). Because the defining characteristics of this illness are fatigue and intolerance for physical activity, it might seem reasonable to use an index of physical functioning to more objectively quantify the level of patient dysfunction and help facilitate uniformity of patient samples. In disease states involving cardiovascular, pulmonary, or metabolic disorders, cardiopulmonary exercise tests (CPX) using maximal oxygen uptake ($\dot{V}O_{2max}$) as a measure of functional capacity are routinely administered to assess the degree of limitation in function and the level of impairment imposed by the disease. Recently CPX testing has been applied to CFS as it has classically been applied to other disease states. Studies evaluating the ability of CFS patients to perform physical work using standardized exercise tests have generated conflicting results. Some researchers report that the aerobic capacity of CFS patients is within the normal range (25,30,35), whereas others find a reduced aerobic capacity compared with healthy subjects (8,11,17,29). Possible explanations for these equivocal findings may include the heterogeneity of CFS patient populations and problems associated with the compromised exercise capacity of some patients. In rehabilitation studies involving exercise, patients are generally high functioning, able to attend outpatient workout sessions, and likely represent less than 10% of CFS cases (31). It is also the case that the exercise-induced pain experienced by many CFS patients can encourage a belief that physical activity is dangerous and possibly associated with organ damage (13). This may be one reason for the high dropout rates found in many exercise studies involving CFS patients (38). A number of cardiac abnormalities have also been identified in CFS patients that may not be apparent with standard 12-lead electrocardiograms (7,22,23). It is suggested that these may result from persistent herpes virus infections and that variations in herpes virus causality could explain the patient heterogeneity in CFS (21). Among the herpes viruses, Epstein-Barr virus (EBV) has been linked to both mild and severe cardiac dysfunction (37). It is possible that virally mediated cardiac abnormalities underlie the inability of some CFS patients to meet accepted criteria for maximal effort during exercise

testing. Patients unable to meet these criteria are often excluded from research involving exercise tests (17).

One aspect of exercise testing notably absent from the CFS research literature is its potential for subclassifying CFS patients based upon their functional status. Such classification could provide for stratification of patients involved in research studies, helping to control for patient differences. Further, assessment of functional capacity may assist physicians when prescribing treatment for CFS. The purpose of this study is to examine the results of exercise testing from a large population of patients with CFS. These findings may provide insight to the mechanisms underlying fatigue, and aid in the treatment of CFS.

METHODS

Appropriate institutional review procedures and documentation of informed written consent were completed before commencement of the study.

Subjects (ages 19–60 yr) comprised the first 189 persons (137 females, 52 males) with CFS recruited for a multicenter phase-III clinical trial involving treatment with the immunomodulatory drug Ampligen[®] (32). Recruitment for the study was through physician referral of individuals with a confirmed and rigorous diagnosis of CFS according to the criteria established by Holmes et al. (16). Excluded were individuals with concurrent medical disorders, or who had been treated with drugs that modulate the immune, cardiovascular, or respiratory systems within 6 wk of testing, and anyone with a condition inhibiting their ability to perform the graded exercise test. All subjects signed an informed consent document before beginning testing. Subjects were instructed to avoid food, alcohol, and caffeine for at least 3 h before testing; they were also asked to avoid significant exertion or exercise for 24 h before testing.

Procedure. Data were collected by an exercise physiologist at 12 testing sites across the United States. For purposes of quality assurance and data consistency all testing was performed by the same exercise physiologist using the same portable testing equipment excepting the treadmill. All equipment (including the treadmill) was calibrated on-site before and after each exercise test and a shortened incremental exercise self-test performed by the exercise physiologist with obtained values compared between sites and with laboratory values.

The entire procedure for exercise testing was explained in detail to each patient before testing. Subjects were fitted with ECG electrodes for monitoring of heart rhythm, a mask and headgear for collection of expired air, and a pulse oximeter for monitoring arterial oxygen saturation. All subjects were allowed to walk briefly (less than 1 min) on the treadmill to allow them to feel comfortable. Workload was increased incrementally every 2 min using a protocol created for testing disabled persons (Table 1) (32). Breath-by-breath measurements of oxygen consumption and carbon dioxide production were collected using an Oxycon Alpha gas analysis system (Jaeger, Würzburg, Germany). The volume sensor was calibrated using a 1-L pump, and gas

TABLE 1. Exercise testing protocol.

Time (min)	Speed (mph)	Grade (%)
0-2	2	0
2-4	2	3
4-6	2	6
6-8	2	9
8-10	2	12
10-12	2	15
12-14	2	18
14-16	2	21
16-18	3	21
18-20	4	21
20-22	5	21

analyzers were calibrated using known gas concentrations (5% CO₂; balance N₂). Complete details of this procedure have been described elsewhere (32,34). Rating of perceived exertion (RPE) (2) was collected every minute, and blood pressure was taken manually every 2 min.

Patients were encouraged to continue with the test for as long as they felt able or until they could no longer maintain position on the treadmill. Continuous ECG monitoring was performed throughout the test and testing terminated if signs of cardiac ischemia or arrhythmias were observed (1). In an effort to guard against problems associated with failure to give maximal effort during testing, all patients performed at least two exercise tests, 2 wk apart. A third test was performed if duration for the first two tests differed by more than 10%. The highest value for oxygen consumption obtained from the tests is reported.

Values recorded for peak oxygen consumption were compared with the severity of impairment index developed by the American Medical Association (14) that utilizes exercise capacity to quantify level of impairment for the whole person. The following values for peak oxygen consumption (mL·kg⁻¹·min⁻¹) were used to categorize subjects: no impairment $\dot{V}O_2 > 25$, mild impairment $\dot{V}O_2$ between 20 and 25, moderate impairment $\dot{V}O_2$ between 15 and 20, and severe impairment $\dot{V}O_2 < 15$. Predicted oxygen consumption was calculated using normative equations based on gender, age, height, and body weight (32). Not all patients met accepted criteria for maximal physiological effort. Although these patients may have attained a psychological rather than physiological maximum, it was apparent during testing that from their perspective maximal effort was given. To fully explore differential responses to exercise testing among CFS patients, it was felt important to include them in the study.

Statistical analysis. Pearson product moment correlation coefficients ranged from 0.02 to 0.77 among the dependent variables: age, body mass index, percentage of predicted $\dot{V}O_2$, resting and peak heart rates, resting and peak systolic blood pressure, respiratory quotient (RQ), and rating of perceived exertion. With no evidence of multicollinearity, i.e., any correlation above 0.9 (15), all variables were entered into a one-way MANOVA to determine differences between impairment categories. As the follow-up to a significant multivariate effect, individual one-way ANOVA analyses were performed for each dependent variable. When significance occurred, Scheffé *post hoc* tests were used to

identify the source of the significance. Significance levels were set at $P < 0.05$ for the initial multivariate analysis. To protect against Type-I errors, subsequent significance levels were adjusted using the Bonferroni procedure: dividing alpha by the number of follow-up comparisons to be made ($0.05/9 = 0.005$) (33).

In light of the physical differences between genders, descriptive statistics were generated to compare males and females at each impairment level for the variable percentage difference between measured values and age- and gender-predicted values for peak oxygen consumption. Because of unequal gender distribution between impairment levels, no further analyses were performed for these data.

Data are presented as mean \pm SE. All statistical analyses were performed using SPSS 10.0 software for Windows operating systems (Statistical Package for the Social Sciences, Inc., Chicago).

RESULTS

A significant multivariate effect was found between impairment levels for a linear combination of the dependent variables, Wilks' $\Lambda = 0.32$, $F(9,179) = 9.27$, $P < 0.001$. Follow-up univariate analyses confirmed this effect for the dependent variables: percentage of predicted $\dot{V}O_2$ $F(3,185) = 59.34$, $P < 0.001$; peak heart rate $F(3,185) = 28.47$, $P < 0.001$; peak systolic blood pressure $F(3,185) = 6.89$, $P < 0.001$; and respiratory quotient $F(3,185) = 10.51$, $P < 0.001$. No significant differences between impairment levels were observed for age, body mass index (BMI), resting heart rate, resting systolic blood pressure, or rating of perceived exertion (RPE) (all $P > 0.005$). Scheffé *post hoc* analyses of the main effects revealed significant differences between each impairment level for percentage of predicted $\dot{V}O_2$ and peak heart rate with an inverse relationship between both variables and severity of impairment. For peak systolic blood pressure the "mild", "moderate", and "severe" levels were significantly different from each other. Peak systolic blood pressure of the no impairment category differed significantly from the "moderate" and "severe" categories but was not significantly different from that of the "mild" category. Again, an inverse relationship between peak systolic blood pressure and severity of impairment was observed. The only significant difference for RQ was between the no impairment group and all other impairment levels (see Table 2).

Actual peak oxygen consumption ranged from 39% to 81% of the values predicted by normative equations (36). Approximately 49% of this population met AMA guidelines for moderate to severe functional impairment. Compared with the males, the women achieved actual values for peak $\dot{V}O_2$, which were closer to their predicted values across all impairment categories (see Table 3).

TABLE 2. Subject characteristics by impairment level (mean \pm SE).

	No Impairment (m = 15, f = 5)	Mild Impairment (m = 21, f = 46)	Moderate Impairment (m = 13, f = 59)	Severe Impairment (m = 3, f = 17)
Age (yr)	40.5 \pm 1.7	42.7 \pm 1.1	43.3 \pm 1.1	47.2 \pm 2.1
BMI (kg·m ⁻²)	29.1 \pm 0.1	29.0 \pm 0.1	29.1 \pm 0.9	29.4 \pm 0.2
$\dot{V}O_2$ peak (mL·kg ⁻¹ ·min ⁻¹)	30.3 \pm 0.9	22.1 \pm 0.2	17.2 \pm 0.2	12.3 \pm 0.5
$\dot{V}O_{2\text{peak}}$ predicted (%)*	80.7 \pm 2.3	65.2 \pm 1.6	51.3 \pm 1.5	38.7 \pm 2.9
Resting HR (beats·min ⁻¹)	73 \pm 2	75 \pm 1	76 \pm 1	76 \pm 3
HR _{peak} * (beats·min ⁻¹)	163 \pm 4	147 \pm 2	133 \pm 2	117 \pm 4
Resting SBP (mm Hg)	114 \pm 3	115 \pm 2	117 \pm 2	121 \pm 3
SBP _{peak} * (mm Hg)	161 \pm 4	152 \pm 3	144 \pm 3	137 \pm 5
RQ _{peak} *	1.16 \pm 0.02	1.07 \pm 0.02	1.02 \pm 0.01	1.02 \pm 0.03
RPE _{peak}	18.9 \pm 0.3	18.6 \pm 0.2	18.2 \pm 0.2	17.7 \pm 0.4

* $P < 0.001$.

m, males; f, females.

DISCUSSION

A primary goal of this study was to examine the differences in exercise capacity within a group of patients diagnosed with CFS. The results from exercise testing clearly demonstrate that despite a common diagnosis, the functional capacity of CFS patients may range from no impairment to severely impaired. This study supports the stratification of patients based on quantifiable measures of physiological response to exercise. Stratifying in this way delineates subsets of patients based on their levels of functional impairment. Such differentiation may add to understanding of this disorder and elucidate research findings.

More women than men are diagnosed with CFS, previous researchers have demonstrated a ratio of approximately three women diagnosed for every male (3). In this population of patients, the overall ratio is between two and three women to every man. However, the ratio of females to males is even greater in the “moderate” (5:1) and “severe” (6:1) categories. Although the AMA disability criteria make no distinctions between genders, it is noteworthy that within each impairment category the women consistently achieved a peak $\dot{V}O_2$ that was closer to their maximal predicted values. This inevitably raises the issue of possible gender bias in disability classification. It is unclear whether this has any significance for reports of greater functional disability among women with CFS compared with men (19). Nevertheless, considering the evidence of other gender-related differences in the outcomes of CFS (3), it may be prudent to further explore the relationship between gender, exercise capacity, and CFS.

If criteria for maximal effort based on attainment of age-predicted maximal heart rate and/or a respiratory quotient of 1.09 were employed for this group, many of the subjects would be removed from the analysis. With the exception of the no impairment group, most subjects failed to meet the accepted criteria for maximal effort. However patient ratings of perceived exertion were “very hard” to “very, very hard.” Additionally, only subjects who performed

at least two exercise tests where duration did not differ by more than 10% and gave maximal effort as determined by the testing technician were included in the study. In other studies, it has been demonstrated that many CFS patients fail to meet criteria for maximal effort based on heart rate (4). Excluding such patients would preclude comparison between other indices of physical functioning across disability levels. It is also the case that accepted criteria for maximal effort were developed for otherwise healthy individuals and many not be appropriate for use with CFS patients. Although it is possible that the poor exercise performance of some CFS patients is due to lack of effort, it was felt that the multiple testing protocol employed in this study was sufficient to ensure that the results obtained accurately reflect patients’ functional capacities.

Although there were no significant differences for resting heart rate between disability levels, the peak heart rate obtained during exercise showed progressively decreasing values for the more impaired groups. A similar trend was also observed for the systolic blood pressure response. The blunted heart rate and blood pressure responses in the “mild” through “severe” groups are similar to those seen in chronic heart failure. Although the presence of heart disease had been ruled out for all the patients in this study as part of the original CFS diagnosis, the tests administered may have been insufficient to detect the less apparent cardiac involvement found in some CFS patients (21). An alternative reason for the chronotropic incompetence observed in response to exercise may be abnormal sympathoadrenal activity. Previous research has shown that CFS patients exhibit a reduced response to stress and attenuated activation of the sympathetic nervous system (5,6). Interestingly, this is the first study we know of that points to a possible relationship between the degree of functional limitation and degree of activation of the cardiovascular system where the most functionally disabled patients exhibit the more compromised cardiac response.

TABLE 3. Measured and predicted values for peak $\dot{V}O_2$ by gender and impairment level (mean \pm SE).

	No Impairment	Mild Impairment	Moderate Impairment	Severe Impairment
Males, $\dot{V}O_2$ predicted (%)	73.3 \pm 3.1 N = 15	56.1 \pm 2.6 N = 21	46.2 \pm 3.3 N = 13	30.0 \pm 6.8 N = 3
Females, $\dot{V}O_2$ predicted (%)	88.0 \pm 3.1 N = 15	69.3 \pm 1.8 N = 46	52.4 \pm 1.5 N = 59	40.2 \pm 2.9 N = 17

CONCLUSIONS

It is apparent from this study that given the current CDC diagnostic criteria (12) any group of CFS patients may respond differently to exercise testing. This lack of uniformity in patient samples has been a major impediment to the development of a treatment for CFS (35). Stratifying CFS patients by disability category is one way of avoiding the problems associated with the broad ranging and subjective nature of the current CFS diagnostic criteria. The results from exercise testing can be used to differentiate between groups of patients all of whom present symptoms consistent with CFS. It may also be possible to speculate on the etiology and pathogenesis of CFS, at least as it is manifest in some patients, using the results of standardized exercise testing. Stratifying patients based upon the AMA guidelines for functional impairment revealed unique cardiovascular profiles for the more impaired patients with respect to heart rate and blood pressure responses during exercise. With no history of heart failure or cardiac myopathy among these patients, their responses are consistent with cardiac autonomic dysfunction. However, it may not be possible to

completely rule out other cardiac pathology without more exhaustive testing. Alternative explanations for their reduced exercise capacities may range from psychological abnormalities, to neuroendocrinological or metabolic dysfunction, to postviral immune system activation. Although exploration of such issues is beyond the scope of this article, it is clear that variability among CFS patients is an important research issue in addition to consideration of differences between CFS patients and healthy controls. It is also apparent that whatever its pathogenesis, many CFS patients are subject to significant impairment as a result of this condition.

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