**Discriminative Validity of Metabolic and Workload Measurements for Identifying People With Chronic Fatigue Syndrome**

Christopher R. Snell, Staci R. Stevens, Todd E. Davenport and J. Mark Van Ness

*PHYS THER.* 2013; 93:1484-1492.
Originally published online June 27, 2013
doi: 10.2522/ptj.20110368

Research Report

# Discriminative Validity of Metabolic and Workload Measurements for Identifying People With Chronic Fatigue Syndrome

Christopher R. Snell, Staci R. Stevens, Todd E. Davenport, J. Mark Van Ness

C.R. Snell, PhD, Department of Sport Sciences, University of the Pacific, Stockton, California, and Workwell Foundation, Ripon, California.

S.R. Stevens, MA, Workwell Foundation.

T.E. Davenport, PT, DPT, OCS, Department of Physical Therapy, University of the Pacific, 3601 Pacific Ave, Stockton, CA 95211 (USA), and Workwell Foundation. Address all correspondence to Dr Davenport at: tdavenport@pacific.edu.

J.M. Van Ness, PhD, Department of Sport Sciences, University of the Pacific, and Workwell Foundation.

[Snell CR, Stevens SR, Davenport TE, Van Ness JM. Discriminative validity of metabolic and workload measurements for identifying people with chronic fatigue syndrome. *Phys Ther.* 2013;93:1484–1492.]



Published Ahead of Print: June 27, 2013
Accepted: June 23, 2013
Submitted: October 27, 2011

**Background.** Reduced functional capacity and postexertion fatigue after physical activity are hallmark symptoms of chronic fatigue syndrome (CFS) and may even qualify for biomarker status. That these symptoms are often delayed may explain the equivocal results for clinical cardiopulmonary exercise testing in people with CFS. Test reproducibility in people who are healthy is well documented. Test reproducibility may not be achievable in people with CFS because of delayed symptoms.

**Objective.** The objective of this study was to determine the discriminative validity of objective measurements obtained during cardiopulmonary exercise testing to distinguish participants with CFS from participants who did not have a disability but were sedentary.

**Design.** A prospective cohort study was conducted.

**Methods.** Gas exchange data, workloads, and related physiological parameters were compared in 51 participants with CFS and 10 control participants, all women, for 2 maximal exercise tests separated by 24 hours.

**Results.** Multivariate analysis showed no significant differences between control participants and participants with CFS for test 1. However, for test 2, participants with CFS achieved significantly lower values for oxygen consumption and workload at peak exercise and at the ventilatory or anaerobic threshold. Follow-up classification analysis differentiated between groups with an overall accuracy of 95.1%.

**Limitations.** Only individuals with CFS who were able to undergo exercise testing were included in this study. Individuals who were unable to meet the criteria for maximal effort during both tests, were unable to complete the 2-day protocol, or displayed overt cardiovascular abnormalities were excluded from the analysis.

**Conclusions.** The lack of any significant differences between groups for the first exercise test would appear to support a deconditioning hypothesis for CFS symptoms. However, the results from the second test indicated the presence of CFS-related postexertion fatigue. It might be concluded that a single exercise test is insufficient to reliably demonstrate functional impairment in people with CFS. A second test might be necessary to document the atypical recovery response and protracted fatigue possibly unique to CFS, which can severely limit productivity in the home and workplace.

The absence of reliable diagnostic laboratory tests or biomarkers often presents significant problems for people with chronic fatigue syndrome (CFS), treating clinicians, and the CFS research community. The nature of conditions characterized by chronic fatigue and pain, such as CFS and fibromyalgia, a common comorbidity, poses a special challenge for physical therapists,[1] in part because fatigue is often associated with deconditioning. Exercise, the logical prescription for physical therapists to use in treating fatigue related to deconditioning, often is not well tolerated by people with CFS. In addition, CFS may be undiagnosed or misdiagnosed by a physician before referral for physical therapy, which places physical therapists at the forefront of recognition and management of individuals with CFS.[2] Although extreme fatigue is a primary symptom in the 3 most commonly used CFS case definitions (the International Chronic Fatigue Syndrome Study Group case definition,[3] the 2003 Canadian clinical case definition,[4] and the Oxford criteria[5]), none operationalizes fatigue or indicates how it should be assessed. It is clear that the development of objective measurements that can delineate symptoms, assist in clinical evaluation, and provide an estimate of prognosis should be of paramount importance.

As a corollary to extreme fatigue in CFS, postexertion malaise (PEM), or exacerbation of symptoms after physical exertion, is considered one of the most common and recognizable aspects of the illness.[6,7] The Canadian consensus document on CFS goes so far as to mandate evidence of symptom expression after physical activity.[4] The presence of postexertion symptoms in the clinical presentation of CFS suggests that cardiopulmonary exercise testing (CPET) can be reliably used to elicit symptoms of CFS while also serving as both an indicator of clinical status and a quantifiable model of physical exertion. Physical therapists are trained to administer and interpret CPET, in which objective measurements are used for the clinical evaluation of undiagnosed exercise intolerance and the determination of functional capacity and impairment. Data obtained from CPET can provide valuable diagnostic and prognostic information regarding outcomes of disease.[8] If physiological parameters that correlate with CFS can be identified through CPET, physical therapists may be able to use them to attempt to diagnose the illness. Because CPET is used to assess function, it may be particularly helpful for physical therapists who evaluate and treat people with illnesses that limit their abilities to perform functional activities.[9]

Previous research comparing exercise test performance in people with CFS and people who do not have a disability is equivocal, with some studies showing lower performance in people with CFS[10] and others showing no difference between the groups.[11] In addition to the patient heterogeneity and small sample sizes that are issues in much CFS research, exercise studies are highly variable in both the protocols and the measurements used. A recent systematic review of the available literature in this area concluded that, on balance, the evidence suggested a reduced physiological exercise capacity in people with CFS.[12] However, in only a few studies were maximal exercise tests used and gas exchange data collected.[12]

The reproducibility of both metabolic and work intensity measurements obtained during CPET is well documented in people who do not have a disability,[8] whereas test-retest decrements in metabolic and workload measurements have been obtained in people with CFS.[13–15] Among all fatiguing conditions, CFS is thought to be unique because of a limited ability to reproduce metabolic and workload measurements on repeat maximal CPET.[15,16] Indeed, most people who are sedentary but otherwise healthy recover from a maximal exercise test within 24 hours. However, for people with CFS, fatigue persists at levels close to those reported immediately after exercise for 24 hours and beyond.[15,17,18] Taken together, these observations suggest the potential importance of metabolic and workload measurements obtained during serial CPET for differentiating people with CFS from people who do not have a disability. However, the discriminative validity of metabolic and workload measurements obtained during serial CPET for such differentiation remains unknown.

The purpose of this study was to establish the discriminative validity of objective measurements obtained during CPET for distinguishing people with CFS from people who do not have a disability but are sedentary. To control for potential individual differences in preparation for testing and the cyclical nature of CFS symptoms, we used a dual-test paradigm comprising 2 CPET sessions separated by 24 hours. We hypothesized that an exacerbation of symptoms after the first test would be reflected in physiological responses to the second test.

## Method

### Participants

A sample of convenience consisting of 51 women with CFS and 10 women who served as a control group participated in this study. Most exercise test data have indicated that gas exchange measurements are highly reproducible within a given individual if testing methods are consistent.[8] Given these data and with CFS as the focus of the study, the disparity in sample size

was deemed acceptable. The women were either recruited specifically as research participants or referred by a treating physician for functional assessment. Efforts were made to match participants with CFS with control participants for age and body mass index. All participants with CFS met the criteria established by Fukuda et al[3] for the diagnosis of CFS. In addition, all participants with CFS reported exacerbation of symptoms after physical activity as a specific aspect of their diagnoses. Both participants with CFS and control participants were sedentary, as defined by the American College of Sports Medicine/American Heart Association (ie, not participating in a regular exercise program or not accumulating 30 minutes or more of moderate physical activity on most days of the week).[19,20]

## Procedure

After informed consent was obtained, the entire procedure for exercise testing was explained in detail to each participant. Aerobic capacity was assessed by use of an electronically braked Ergoline 800 stationary cycle ergometer (CareFusion Corp, San Diego, California) with a ramping protocol designed to reach peak work rates in 8 to 12 minutes.

The protocol included 3 minutes of rest followed by 1 minute of unloaded cycling before the exercise test. Participants were asked to maintain a pedaling cadence of 60 to 80 rpm throughout the test. For the test, workload was increased progressively at a rate of 5 W/20 s (15 W/min), and participants were encouraged to pedal for as long as possible. Breath-by-breath gas samples were collected with a comfortably fitted Hans Rudolph face mask (Hans Rudolph Inc, Shawnee, Kansas) and analyzed throughout the test with a Jaeger Oxycon Alpha metabolic cart (CareFusion Corp). Participants remained seated on the ergometer, and recovery was monitored for 2 to 5 minutes. Care was taken to ensure complete safety during the entire procedure. Continuous electrocardiographic monitoring of heart rate (12 lead) and measurement of blood pressure every 2 minutes took place during the test.

Gas exchange data at peak exercise were recorded. All participants achieved a respiratory exchange ratio (RER) of greater than or equal to 1.1, indicating excellent effort during testing.[8] In addition to an RER of greater than or equal to 1.1, all participants met at least 1 other criterion for determining peak effort (ie, a plateau in oxygen consumption, a rating of perceived exertion of >17, or a heart rate of >85% of the age-predicted maximum), according to standard CPET interpretation procedures.[21] Submaximal responses at the ventilatory threshold (VT) were determined with the V-slope method.*,[22] In addition to the value identified automatically by the equipment, 2 experienced reviewers validated the VT visually. The second reviewer was unaware of participant status. Subsequent to the initial exercise test, all procedures were repeated 24 hours later.

## Data Analysis

To determine whether exercise performance variables could be used to reliably and accurately discriminate between participants with CFS and control participants who were sedentary, we entered peak oxygen consumption, oxygen consumption at the VT, peak workload, and workload at the VT as the dependent variables in a factorial multivariate analysis of variance (group × test). Post hoc, descriptive discriminant function analyses were then used to determine the variables that best differentiated between groups at each level of the test (ie, test 1 and test 2). On the basis of the test-retest effect shown in previous research, between-group differences across tests may be diagnostically relevant.[13,14] Thus, in the present study, if a positive group × test interaction was identified by a multivariate analysis of variance, an additional investigation, with separate discriminant function analyses for test 1 and test 2, was undertaken to determine the source of the difference. This level of analysis would provide the opportunity to establish the clinical importance of between-group differences in each test that could be diagnostically relevant. Discriminant function analyses can be sensitive to sample size, but both the ratio of total sample to discriminator variables (15:1) and the ratio of group samples to discriminator variables for the smallest group (3:1) were within acceptable ranges.[23]

To aid in the interpretation of results, we conducted post hoc F tests for each exercise performance variable.[24] A Bonferroni-type adjustment was made to the test alpha level (alpha=.0125) to counteract the potential for an inflated error rate due to multiple F tests. All statistical analyses were performed with SPSS 13.0 software for Windows operating systems (SPSS Inc, Chicago, Illinois).

## Role of the Funding Source

This study was funded, in part, by a grant from the Chronic Fatigue and Immune Dysfunction Association of America.

# Results

No significant differences were found between participants with CFS and control participants for age, height, weight, or body mass index ($P>.05$). Descriptive statistics for physical variables are shown in Table

* The VT is generally accepted as being synonymous with the anaerobic threshold, or the point at which energy production transitions from primarily aerobic to increasingly anaerobic glycolysis.

1. The duration of illness for participants with CFS ranged from 6 months to 30 years (mean duration=11.06 years). Not all participants with CFS were able to recall how they first began to experience symptoms, but 25 participants reported a sudden onset and 13 participants reported a gradual onset.

The duration of testing was limited by extreme fatigue,[22] but all tests were within the optimum range of 8 to 12 minutes for fatigue-limited exercise.[8] All participants cited leg pain and muscle fatigue as the reason for ending the tests, regardless of group. Correlations among the dependent variables ranged from $R$=.427 to $R$=.699, fulfilling the requirement for correlations that are moderate or lower in magnitude.[23] A significant Box's M test result ($P$<.001) indicated that homogeneity could not be assumed for the variance-covariance matrixes across cells formed by the between-subject effects. Therefore, the Pillai trace test statistic was used to interpret significance because it is considered the most conservative and robust in the presence of unequal multivariate distributions.

The results of a multivariate analysis of variance showed a significant group × test interaction (Pillai trace=.113; F=3.47; $df$=4,115; $P$=.010; power=.847) for the combined dependent variables peak oxygen consumption, oxygen consumption at the VT, peak workload, and workload at the VT. The test effect was not significant (Pillai trace=.086; F=2.09; $df$=4,115; $P$=.086; power=.606) (Tab. 2).

### Test 1

A nonsignificant Box's M test ($P$=.103) indicated that homogeneity of variance-covariance could be assumed; therefore, the Wilks Λ test statistic was used to interpret significance. No variables from the first test qualified for discriminant analysis (Wilks Λ=.856, $\chi^2$=8.84, $df$=4, N=61, $P$=.065). Univariate comparisons of group means indicated a significant group difference for peak workload (F=6.11; $df$=1,59; $P$=.005). There were no other significant group differences ($P$>.0125) (Figs. 1 and 2).

**Table 1.**
Physical Data by Group

| Characteristic | $\bar{X}$ (SD) for: CFS[a] Group (n=51) | Control Group (n=10) | P |
|---|---|---|---|
| Age, y | 46.29 (8.01) | 40.80 (7.69) | .053 |
| Height, m | 1.65 (0.09) | 1.61 (0.10) | .174 |
| Weight, kg | 70.66 (14.33) | 74.39 (9.03) | .433 |
| Body mass index, kg/m$^2$ | 25.96 (4.95) | 28.99 (4.24) | .076 |

[a] CFS=chronic fatigue syndrome.

### Test 2

A nonsignificant Box's M test ($P$=.252) indicated that homogeneity of variance-covariance could be assumed; therefore, the Wilks Λ test statistic was used to interpret significance. Discriminant analysis generated 1 significant function that differentiated between participants with CFS and control participants (Wilks Λ=.516, $\chi^2$=37.71, $df$=4, N=61, $P$<.001). The diagnosis of CFS was found to account for 48% of the function variance. Standardized function coefficients and correlation coefficients showed that workload at the VT contributed the most to the difference between groups; peak workload made the next largest contribution. Classification results revealed that 49 of 51 participants with CFS and 9 of 10 control participants were correctly classified. For the total sample, 95.1% were correctly classified. Cross-validation derived 90.2% accuracy for the total sample. The means of the discriminant functions were consistent with these results. For control participants, the function mean was 2.15, whereas for participants with CFS, the function mean was −0.422. Univariate analyses comparing group means for each variable generally concurred with this interpretation, although the group means for peak oxygen consumption were not significantly different at the Bonferroni-adjusted alpha level ($P$=.026) (Tab. 3).

## Discussion

Optimal physical therapist examination, evaluation, and intervention for people with CFS remain challenged by a lack of validated diagnostic measurements and a limited understanding of the underlying pathophysiology of the condition. The present study was designed to examine the validity of oxygen consumption and workload measurements to differentiate between participants with CFS and matched control participants (who did not have a disability). Unlike control participants and consistent with previous research,[25,26] participants with CFS were unable to reproduce their test 1 performance on test 2.[13,14,18,19] The decreased test 2 performance for participants with CFS could be used diagnostically as an objective indicator of an abnormal postexertion response and possibly even a biomarker for the condition. The performance decrement between tests for participants with CFS was most apparent for workload, particularly workload at the VT. Attainment of the VT was a further indication (in addition to an RER of ≥1.1) that group differences were not due to a lack of effort. The VT

**Table 2.**
Exercise Performance Variables by Group and Test[a]

| Variable | Test 1 | | | | | Test 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CFS Group (n=51) | | Control Group (n=10) | | Effect Size (Cohen *d*) | CFS Group (n=51) | | Control Group (n=10) | | Effect Size (Cohen *d*) |
| | $\bar{X}$ (SD) | 95% CI | $\bar{X}$ (SD) | 95% CI | | $\bar{X}$ (SD) | 95% CI | $\bar{X}$ (SD) | 95% CI | |
| $\dot{V}O_2$peak, mL/kg/min | 21.51 (4.09) | 20.34–22.71 | 25.04 (4.41) | 22.35–27.73 | 0.8 | 20.44 (4.47) | 19.25–21.63 | 23.96 (4.30) | 21.27–26.65 | 0.8 |
| $V_{TO_2}$, mL/kg/min | 12.74 (2.85) | 11.92–13.55 | 13.83 (2.79) | 12.00–15.67 | 0.4 | 11.36 (2.91) | 10.39–12.01 | 14.12 (3.26) | 12.29–15.96 | 0.9 |
| WLpeak, W | 109.57 (28.86) | 102.36–116.78 | 137.20 (23.16) | 120.92–153.48 | 1.1 | 101.63 (30.66) | 96.89–111.31 | 140.00 (24.94) | 123.72–156.28 | 1.4 |
| VTWL, W | 49.51 (20.40) | 44.53–54.88 | 58.00 (16.71) | 46.32–69.68 | 0.5 | 22.20 (18.05) | 16.12–26.46 | 63.50 (19.53) | 51.82–75.18 | 2.2 |
| RERpeak | 1.34 (0.17) | 1.28–1.38 | 1.33 (0.9) | 1.26–1.39 | 0.1 | 1.31 (0.12) | 1.27–1.34 | 1.38 (0.12) | 1.29–1.46 | 0.6 |

[a] CFS=chronic fatigue syndrome, CI=confidence interval, $\dot{V}O_2$peak=volume of oxygen consumed at peak exertion, $V_{TO_2}$=volume of oxygen consumed at ventilatory threshold, WLpeak=workload at peak exertion, VTWL=workload at ventilatory threshold, RERpeak=respiratory exchange ratio at peak exertion.

represents the point at which energy derived from anaerobic metabolism becomes the predominant metabolic pathway. It is an important measure in CPET because it represents the onset of fatigue. Because of an increased reliance on glycolytic metabolism and an increased production of lactic acid, work intensity cannot be maintained, resulting in the reduction or cessation of activity.

The VT is also an important measure for understanding the activity limitations in CFS.[27] Under normal circumstances, most activities of daily living require energy levels below the VT. However, if the VT occurs at very low levels of oxygen consumption, very low workloads, or both, even normal activities of daily living may exceed the VT. Therefore, it is possible that in CFS the increased stress of requiring anaerobic energy even for normal activities of daily living precipitates the symptom exacerbation seen in PEM. The results of the present study, in context with those of earlier studies, add to a growing body of literature that provides a rationale for physical therapists to use CPET to identify and characterize CFS.

Cardiopulmonary exercise testing, a testing modality that can be applied and interpreted in a skilled manner by physical therapists, permits a thorough assessment of the integrated response to exercise through a comprehensive evaluation of the pulmonary, cardiovascular, hematopoietic, neuropsychological, and musculoskeletal systems.[26] To date, however, few studies have used maximal CPET with gas exchange data collection in people with CFS, and fewer still have used a dual-test paradigm. Thus, the body of literature to guide physical therapists in applying and interpreting CPET for people with CFS is limited. In a recent study in which CPET was combined with gas exchange data collection, people with CFS reached the VT and peak exercise at much lower levels of oxygen consumption than people who served as controls in both tests. The differences were magnified in the second test.[14] Consistent with earlier research,[25] no abnormalities in muscular mitochondrial oxidative phosphorylation were identified. This result led to the conclusion that the poorer performance of people with CFS may have been due to limited oxygen-carrying capacity. This explanation is also viable for the results obtained in the present study and emphasizes the value of physical therapists using a multisystem measurement tool, such as CPET, to understand exercise performance and functional decrements in people with CFS.[26]

Despite being regarded as the most accurate method for assessing function,[21] maximal exercise testing with the measurement of expired gases can be problematic from both procedural and ethical perspectives. When fatigue and pain are primary symptoms, as in both CFS and fibromyalgia syndrome, patients may not be capable of performing a maximal test.[28,29] The ethics of requiring patients to undertake a test likely to exacerbate pain and symptoms also can be questioned.[7]

In light of these significant concerns, several investigators have attempted to develop appropriate submaximal exercise tests for people with CFS. The results of a standardized submaximal ergometer test (the aerobic power test) were found to be subject to high error rates when used to predict peak exercise performance; therefore, this test was deemed to be inappropriate for clinical purposes. Several participants were unable to reach 75% of the age-predicted maximal target heart rate. This finding was cited as a major limiting factor in that study.[29] These results raise concerns about the external validity of

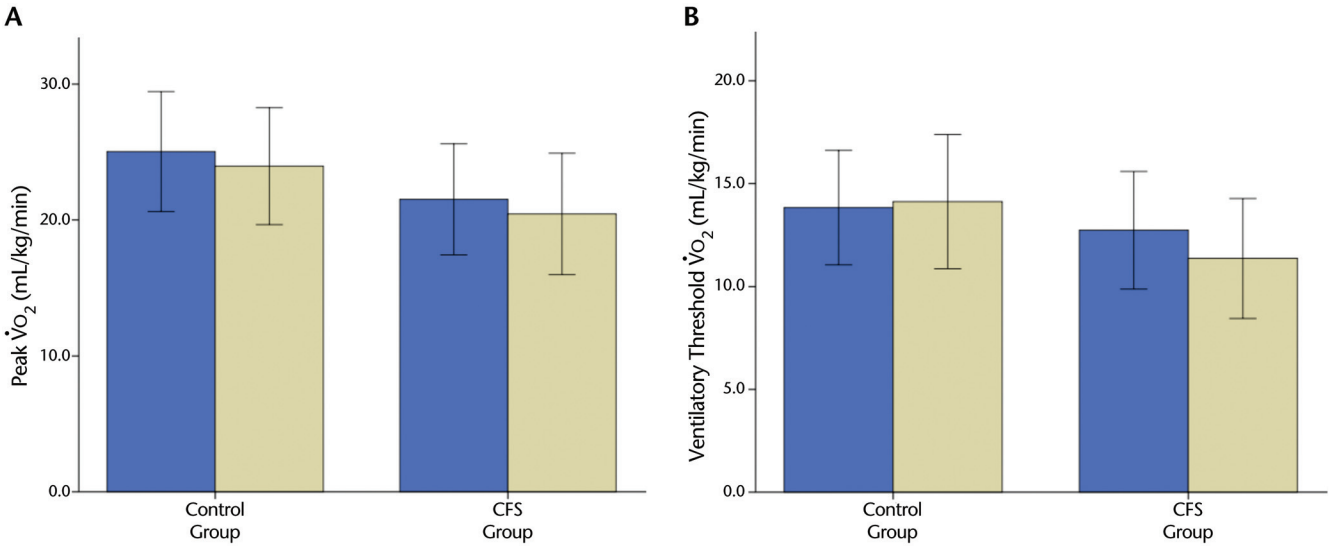


**Figure 1.**
Measurements of oxygen consumption ($\dot{V}O_2$) at peak exercise (A) and at the ventilatory threshold (B) in participants with chronic fatigue syndrome (CFS) and control participants during cardiopulmonary exercise test 1 (blue bars) and cardiopulmonary exercise test 2 (gold bars). Error bars represent 1 standard deviation.

other research using the same protocol to measure physiological responses in people with CFS.[30,31] A more recent study in which the aerobic power test was used as an exercise challenge to study pain and PEM in people with CFS revealed significant differences in the peak RER between the CFS group ($\bar{X}$=1.25) and the control group ($\bar{X}$=0.98).[7] On the basis of accepted criteria for evaluating effort during CPET, a peak RER of greater than 1.10 indicates excellent effort, and a peak RER of less than 1.0 reflects submaximal effort.[8,21] The indication is that the CFS group was working at or close to maximal exertion, whereas the control group was not. These data have important implications for physical therapists because even low-level exercise assessments and interventions can involve nearly maximal exertion by people with CFS.

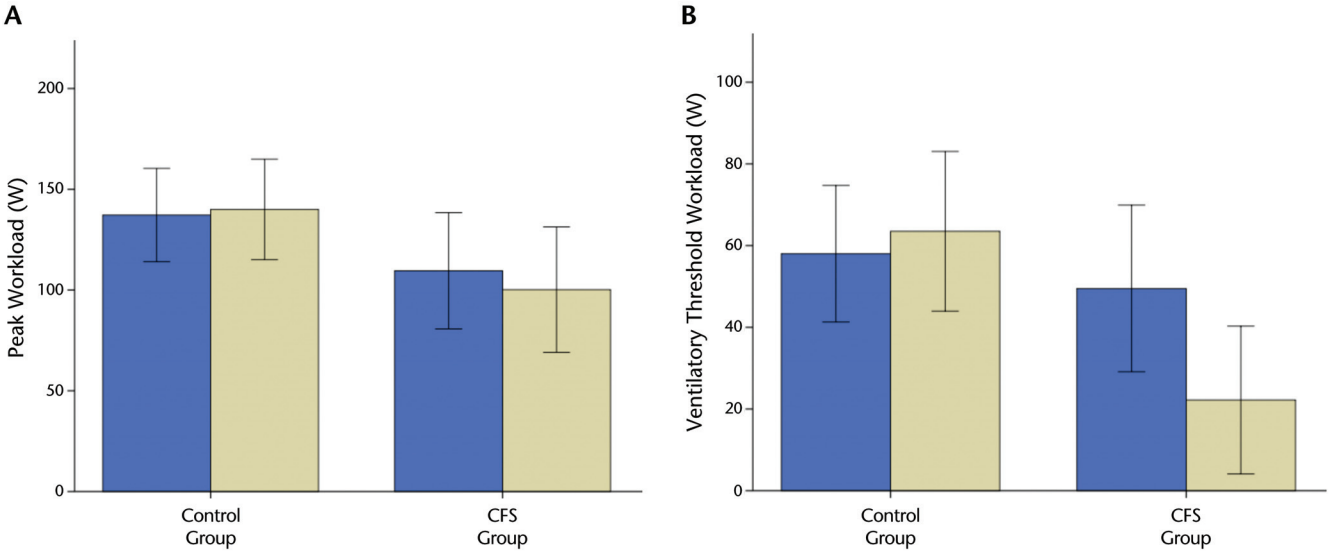


**Figure 2.**
Measurements of workload at peak exercise (A) and at the ventilatory threshold (B) in participants with chronic fatigue syndrome (CFS) and control participants during cardiopulmonary exercise test 1 (blue bars) and cardiopulmonary exercise test 2 (gold bars). Error bars represent 1 standard deviation.

**Table 3.**
Canonical Correlation Coefficients, Standardized Function Coefficients, F Values, and *P* Values for Test 2[a]

| Variable | Canonical Correlation Coefficient With Discriminant Function | Standardized Function Coefficient | F[b] | *P* |
|---|---|---|---|---|
| $\dot{V}O_2$peak, mL/kg/min | .308 | −.308 | 5.23 | .026 |
| $V_{TO_2}$, mL/kg/min | .254 | .375 | 7.78 | .007[c] |
| WLpeak, W | .559 | .563 | 17.54 | <.001[d] |
| VTWL, W | .781 | .877 | 42.57 | <.001[d] |

[a] $\dot{V}O_2$peak=volume of oxygen consumed at peak exertion, $V_{TO_2}$=volume of oxygen consumed at ventilatory threshold, WLpeak=workload at peak exertion, VTWL=workload at ventilatory threshold.
[b] *df*=1,59.
[c] Statistically significant at *P*<.01.
[d] Statistically significant at *P*<.001.

The attainment of RERs exceeding 1.1 by all participants in the present study indicated comparable effort by both groups. In addition, all participants met at least 1 other criterion for peak effort. However, problems of subjectivity and interindividual variability suggest that caution should be exercised when interpreting the highest values obtained as maximal.[21] In this respect, submaximal data may allow more valid comparisons between groups. The analyses indicated that a lower level of oxygen consumption at the VT in test 2 for participants with CFS contributed significantly to the multivariate differences between the groups. Although statistically significant, the mean values did not distinguish between the groups clinically. Both groups would be classified as having moderate to severe impairments on the basis of these data[32] because peak oxygen consumption values for both groups were below the 10th percentile for equivalent population data.[21] A more telling difference was the workload at which each group attained the VT; in test 2, the output for the CFS group was approximately 40 W lower. The deficit in the between-group workload at the VT in test 1 was only approximately 8 W. Physical therapists should be aware that the postexertion state in patients with CFS is characterized by objectively measurable deficits in submaximal metabolism and workload that would be nearly impossible for patients to fabricate.

The etiology of the postexertion reduction in work efficiency observed in the present study remains unclear and warrants further research, especially given that the variables measured in the present study explained almost half of the discriminative function variance. It is possible that synergy of small effects across multiple systems was responsible for the poor exercise performance of participants with CFS in the present study. Lower workloads and levels of oxygen consumption at peak exercise and at the VT are consistent with a reduced oxygen-carrying capacity hypothesis.[26] Possible explanations for this finding include low blood volume[33] and cardiac abnormalities, such as small heart syndrome.[34,35] In the absence of respiratory disease, low oxygen consumption also could result from autonomic dysfunction and reduced ventilation.[36] This symptomatology has been linked to immune dysregulation, like that seen in illnesses such as Guillain-Barré syndrome and multiple sclerosis.[37] It also has been suggested that the choice of an exercise testing protocol can influence the mechanical efficiency of people with CFS.[29] Future studies should examine variables affecting mechanical efficiency across 2 identically administered maximal CPET sessions.

The present study would have benefited from the inclusion of further measurements to minimize the heterogeneity of participants. Current CFS case definitions are suitably vague, such that individual diagnoses can show many clinical differences. The problems of participant heterogeneity in CFS research were discussed in a recent article recommending minimum standards for data elements in CFS studies and consideration of measurements that allow for subgrouping.[38] Functional outcome measures such as those obtained in the present study could provide a way to subgroup study participants. As in much CFS research, participation in the present study was limited to women. Although this is a common approach to controlling for gender bias,[12] it does limit the generalizability of study findings. Tester bias is another potential problem for the present study because 1 of the testers was not unaware of participant status. In an attempt to control for any confounding effects, objective criteria were used to determine data points used in the analyses. For selecting VT data, in addition to the tester, an experienced reviewer unaware of participant status was used to validate the selected values. Lactate measurements would have provided additional validation of the VT and should be considered in future research of this type.

As a quantifiable stressor, CPET has the capacity to reveal abnormalities across multiple systems that may not be apparent at rest. Therefore, it can be of tremendous value to physical therapists for differential diagnosis,

for clinical and functional assessments, and as an indicator of treatment effectiveness. The RER, a measure exclusive to the analysis of expired gases, provides the most accurate and reliable gauge of an individual's effort. The use of this measure avoids problems associated with the use of the age-predicted maximal heart rate, which varies significantly in the general population and can be affected by both medication and pathology.[8] A blunted heart rate response to exercise has been shown in both CFS[39] and fibromyalgia syndrome.[40] Issues of response bias in self-report indictors of effort also are avoided when CPET and RER are used.

For these reasons, it has been recommended that CPET should be a primary consideration in the design of clinical trials with functional endpoints.[8] This recommendation notwithstanding, the value of exercise testing for evaluating therapeutic treatments in people with CFS has been questioned on the basis of a single study in which exercise capacity measurements were used to evaluate cognitive behavioral and graded-exercise–based strategies.[41] Because of their association with psychological hypotheses, deconditioning hypotheses, or both for CFS symptoms, these treatment approaches are subject to considerable controversy within the community of people with CFS. Suffice it to say that if neither of these hypotheses adequately explains the phenomenon of CFS, one would hardly expect to see improved cardiovascular functioning subsequent to such therapies. As the authors of that study indicated, many improvements in health-related quality of life for people with CFS can be achieved without increases in exercise capacity.[41] For example, pacing has been effective in reducing the exertion-related symptoms of CFS in patients unable to exercise because of PEM.[42] These findings do not preclude the use of data obtained through CPET as endpoints in other therapeutic trials or for the purposes of diagnosis and prognosis.

In conclusion, a serial CPET protocol with the measurement of expired gases was efficacious in distinguishing between people with CFS and people who were sedentary but otherwise healthy. As in the only other identified studies in which a dual CPET paradigm with the measurement of expired gases was used,[14,15] participants with CFS showed a decrease in performance on the second test that was not seen in control participants. This functional deficit may provide an objective indication of PEM. Despite considerable patient heterogeneity with respect to illness duration and type of onset, analysis of data from the second test was able to correctly classify 49 of 51 participants with CFS and 9 of 10 control participants. Noninvasive biomarkers for CFS do not currently exist. Physical therapists may consider the use of CPET performance measurements to differentiate between people with CFS and people who do not have a disability but are sedentary. Work efficiency (ie, oxygen consumption and work output) at the VT or anaerobic threshold appears to have diagnostic potential for CFS. Cardiopulmonary exercise testing is a test modality compatible with physical therapist practice patterns and provides a way for the profession to make strong contributions to the diagnosis, treatment, and research of CFS.

All authors provided concept/idea/research design and data collection and analysis. Dr Snell, Dr Davenport, and Dr Van Ness provided writing. Dr Snell and Dr Van Ness provided fund procurement. Dr Snell and Ms Stevens provided facilities/equipment. Dr Davenport provided clerical support. Dr Snell, Ms Stevens, and Dr Davenport provided project management, institutional liaisons, and consultation (including review of manuscript before submission). The authors thank Daniel Peterson, MD, and Jose Montoya, MD, for referring potential study participants. They also gratefully acknowledge all study participants for their valuable contribution.

This study received exempt review approval from the Institutional Review Board at the University of the Pacific, Stockton, California.

Portions of the data were presented at the Combined Sections Meeting of the American Physical Therapy Association; February 8–11, 2012; Chicago, Illinois.

This study was funded, in part, by a grant from the Chronic Fatigue and Immune Dysfunction Association of America.

DOI: 10.2522/ptj.20110368

## References

1 Schachter CL, Busch AJ, Peloso PM, Sheppard MS. Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: a randomized controlled trial. *Phys Ther.* 2003;83:340–358.

2 Griffith JP, Zarrouf FA. A systematic review of chronic fatigue syndrome: don't assume it's depression. *J Clin Psychiatry.* 2008;10:120–128.

3 Fukuda K, Straus SE, Hickie I, et al; International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med.* 1994;121:953–959.

4 Carruthers BM, Jain AK, De Meirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *Journal of Chronic Fatigue Syndrome.* 2003;11:7–115.

5 Sharpe MC, Archard LC, Banatvala JE, et al. A report: chronic fatigue syndrome—guidelines for research. *J R Soc Med.* 1991;84:118–121.

6 Nijs J, Van Oosterwijck J, Meeus M, et al. Unravelling the nature of postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: the role of elastase, complement C4a and interleukin-1beta. *J Intern Med.* 2010;267:418–435.

7 Van Oosterwijck J, Nijs J, Meeus M, et al. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. *J Intern Med.* 2010;268:265–278.

8 Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation.* 2010;122:191–225.

9 American Physical Therapy Association. Today's physical therapist: a comprehensive review of a 21st-century health care profession. Move Forward website. Available at: http://www.moveforwardpt.com. 2012. Accessed March 7, 2012.

**10** De Becker P, Roeykens J, Reynders M, et al. Exercise capacity in chronic fatigue syndrome. *Arch Intern Med.* 2000;160:3270–3277.

**11** Sargent C, Scroop GC, Nemeth PM, et al. Maximal oxygen uptake and lactate metabolism are normal in chronic fatigue syndrome. *Med Sci Sports Exerc.* 2002;34:51–56.

**12** Nijs J, Aelbrecht S, Meeus M, et al. Tired of being inactive: a systematic literature review of physical activity, physiological exercise capacity and muscle strength in patients with chronic fatigue syndrome. *Disabil Rehabil.* 2011;33:1493–1500.

**13** Van Ness JM, Snell CR, Strayer DR, et al. Subclassifying chronic fatigue syndrome through exercise testing. *Med Sci Sports Exerc.* 2003;35:908–913.

**14** Vermeulen RC, Kurk RM, Visser FC, et al. Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. *J Transl Med.* 2010;8:93.

**15** Van Ness JM, Stevens SR, Bateman L, et al. Postexertional malaise in women with chronic fatigue syndrome. *J Womens Health (Larchmt).* 2009;19:239–244.

**16** Davenport TE, Stevens SR, Van Ness MJ, et al. Conceptual model for physical therapist management of chronic fatigue syndrome/myalgic encephalomyelitis. *Phys Ther.* 2010;90:602–614.

**17** Davenport TE, Stevens SR, Baroni K, et al. Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue. *Disabil Rehabil.* 2011;33:2596–2604.

**18** Davenport TE, Stevens SR, Baroni K, et al. Diagnostic accuracy of symptoms characterising chronic fatigue syndrome. *Disabil Rehabil.* 2011;33:1768–1775.

**19** Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007;39:1423–1434.

**20** Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation.* 2007;116:1081–1093.

**21** American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 8th ed. Ambler, PA: Lippincott Williams & Wilkins; 2009.

**22** Wasserman K, Hansen JE, Sue DY, et al. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

**23** Tinsley H, Brown S. *Handbook of Applied Multivariate Statistics and Mathematical Modeling*. Philadelphia, PA: Academic Press; 2000.

**24** Enders CK. Performing multivariate group comparisons following a statistically significant MANOVA. *Measurement and Evaluation in Counseling and Development.* 2003;36:40–56.

**25** McCully KK, Natelson BH. Impaired oxygen delivery to muscle in chronic fatigue syndrome. *Clin Sci.* 1999;97:603–608.

**26** Forman DE, Myers J, Lavie CJ, et al. Cardiopulmonary exercise testing: relevant but underused. *Postgrad Med.* 2010;122:68–86.

**27** Jones DE, Hollingsworth KG, Jakovljevic DG, et al. Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study. *Eur J Clin Investig.* 2012;42:186–194.

**28** Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. *Phys Ther.* 2000;80:782–807.

**29** Nijs J, Zwinnen K, Meeusen R, et al. Comparison of two exercise testing protocols in patients with chronic fatigue syndrome. *J Rehabil Res Dev.* 2007;44:553–559.

**30** Wallman K, Goodman C, Morton A, et al. Test-retest reliability of the Aerobic Power Index test in patients with chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome.* 2003;11:19–32.

**31** Wallman KE, Morton AR, Goodman C, Grove R. Physiological responses during a submaximal cycle test in chronic fatigue syndrome. *Med Sci Sports Exerc.* 2004;36:1682–1688.

**32** Weber KT, Janicki JS, Likoff MJ. Exercise testing in the evaluation of cardiopulmonary disease: a cardiologist's point of view. *Clinics Chest Med.* 1984;5:173–180.

**33** Hurwitz BE, Coryell VT, Parker M, et al. Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function. *Clin Sci.* 2010;118:125–135.

**34** Miwa K, Fujita M. Cardiovascular dysfunction with low cardiac output due to a small heart in patients with chronic fatigue syndrome. *Intern Med.* 2009;48:1849–1854.

**35** Miwa K, Fujita M. Small heart syndrome in patients with chronic fatigue syndrome. *Clin Cardiol.* 2008;31:328–333.

**36** Newton JL, Okonkwo O, Sutcliffe K, et al. Symptoms of autonomic dysfunction in chronic fatigue syndrome. *QJM.* 2007;100:519–526.

**37** Flachenecker P. Autonomic dysfunction in Guillain-Barré syndrome and multiple sclerosis. *J Neurol.* 2007;254(suppl 2):II96–II101.

**38** Jason LA, Unger ER, Dimitrakoff JD, et al. Minimum data elements for research reports on CFS. *Brain Behav Immun.* 2012;26:401–406.

**39** Van Ness JM, Snell CR, Stevens SR. Diminished cardiopulmonary capacity during post-exertional malaise in chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome.* 2008;14:77–85.

**40** da Cunha Ribeiro RP, Roschel H, Artioli GG, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. *Arthritis Res Ther.* 2011;13:R190.

**41** Pardaens K, Haagdorens L, Van Wambeke P, et al. How relevant are exercise capacity measures for evaluating treatment effects in chronic fatigue syndrome? Results from a prospective, multidisciplinary outcome study. *Clin Rehabil.* 2006;20:56–66.

**42** Goudsmit EM, Nijs J, Jason LA, Wallman KE. Pacing as a strategy to improve energy management in myalgic encephalomyelitis/chronic fatigue syndrome: a consensus document. *Disabil Rehabil.* 2012;34:1140–1147.

# Discriminative Validity of Metabolic and Workload Measurements for Identifying People With Chronic Fatigue Syndrome

Christopher R. Snell, Staci R. Stevens, Todd E. Davenport and J. Mark Van Ness

*PHYS THER.* 2013; 93:1484-1492.
Originally published online June 27, 2013
doi: 10.2522/ptj.20110368