

# Diminished Cardiopulmonary Capacity During Post-Exertional Malaise

J. Mark VanNess, PhD  
Christopher R. Snell, PhD  
Staci R. Stevens, MA

**ABSTRACT.** Reduced functional capacity and post-exertional malaise following physical activity are hallmark symptoms of Chronic Fatigue Syndrome (CFS). That these symptoms are often delayed may explain the equivocal results for clinical cardiopulmonary exercise testing with CFS patients. The reproducibility of  $VO_2$ max in healthy subjects is well documented. This may not be the case with CFS due to delayed recovery symptoms.

**Purpose:** To compare results from repeated exercise tests as indicators of post-exertional malaise in CFS.

**Methods:** Peak oxygen consumption ( $VO_2$  peak), percentage of predicted peak heart rate (HR%), and  $VO_2$  at anaerobic threshold (AT), were compared between six CFS patients and six control subjects for two maximal exercise tests separated by 24 hours.

**Results:** Multivariate analysis showed no significant differences between control and CFS, respectively, for test 1:  $VO_2$  peak ( $28.4 \pm 7.2$  ml/kg/min;  $26.2 \pm 4.9$  ml/kg/min), AT ( $17.5 \pm 4.8$  ml/kg/min;  $15.0 \pm 4.9$  ml/kg/min) or HR% ( $87.0 \pm 25.4\%$ ;  $94.8 \pm 8.8\%$ ). However, for test 2 the CFS patients achieved significantly lower values for both  $VO_2$  peak ( $28.9 \pm 8.0$  ml/kg/min;  $20.5 \pm 1.8$  ml/kg/min,  $p = 0.031$ ) and AT ( $18.0 \pm$

---

J. Mark VanNess, Christopher R. Snell and Staci R. Stevens are affiliated with the University of the Pacific, Pacific Fatigue Laboratory, Stockton, CA.

Address correspondence to: J. Mark VanNess, University of the Pacific, Stockton, CA 95211 (E-mail: mvanness@pacific.edu).

The authors thank Betsy Keller, PhD, and her colleagues at Ithaca College for their collaboration and support on this project.

Journal of Chronic Fatigue Syndrome, Vol. 14(2) 2007

Available online at <http://jcfs.haworthpress.com>

© 2007 by The Haworth Press. All rights reserved.

doi:10.1300/J092v14n02\_07

5.2 ml/kg/min;  $11.0 \pm 3.4$  ml/kg/min,  $p = 0.021$ ). HR% was not significantly different ( $97.6 \pm 27.2\%$ ;  $87.8 \pm 9.3\%$ ,  $p = 0.07$ ). A follow-up classification analysis differentiated between CFS patients and controls with an overall accuracy of 92%.

**Conclusion:** In the absence of a second exercise test, the lack of any significant differences for the first test would appear to suggest no functional impairment in CFS patients. However, the results from the second test indicate the presence of a CFS related post-exertional malaise. It might be concluded then that a single exercise test is insufficient to demonstrate functional impairment in CFS patients. A second test may be necessary to document the atypical recovery response and protracted malaise unique to CFS. doi:10.1300/J092v14n02\_07 [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2007 by The Haworth Press. All rights reserved.]

**KEYWORDS.** Serial exercise testing, functional impairment, differential diagnosis

## INTRODUCTION

Chronic Fatigue Syndrome (CFS) is a complex illness characterized by pervasive fatigue, sleep disturbance, neurocognitive problems, joint and muscle pain and numerous other symptoms. One of the most common and recognizable aspects of CFS is often termed “post-exertional malaise,” a worsening of symptoms after physical exertion and prolonged recovery time. Indeed, the cyclical pattern of CFS symptoms may follow from alterations in physical activity with “worse” days following excessive physical activity and “better” days following rest. Individual differences in activity levels and their effect on symptoms may contribute to heterogeneity of patient samples and subsequent variability in clinical findings.

There is a growing body of evidence to support an association between low exercise performance and intracellular immune deregulation in CFS (1,2). Intense training is known to result in temporary immunosuppression and repeated bouts of heavy exercise can lead to the chronic diminution of immune function implicated in overtraining syndrome among athletes (3). CFS and overtraining syndrome share many similarities although, in CFS, the symptom complex can be precipitated by single instances of relatively low-level physical activity. However,

by limiting physical activity and conserving energy CFS patients are often able to effectively control their illness and mitigate symptom expression (4).

There have been a number of CFS studies in which cardiopulmonary exercise testing has been used both to document functional impairment and examine potential abnormalities in physiological function. Results from these studies have been equivocal. Some researchers report that the aerobic capacity of CFS patients is within the normal range (5) whereas others find a reduced aerobic capacity compared to healthy subjects (6). These differences may reflect CFS population differences with respect to illness severity. It is also possible that some CFS patients rest in anticipation of a scheduled exercise test, which may explain their normal performance in certain studies.

The purpose of this study was to explore the use of repeated exercise tests to control for individual differences in preparation for exercise testing and the cyclical nature of CFS symptoms. It was hypothesized that exacerbation of symptoms would follow the first test and be reflected in physiological responses to the second test. The reproducibility of both metabolic measurements and work intensity is well documented for both normal and pathological populations (7). Indeed, a major consideration for test-retest reliability in cardiac patients is that of practice effects where patients may actually improve performance over a series of tests (8).

## **METHODS**

The study procedures followed guidelines for research with human subjects and were approved by the institutional review board. Written informed consent was obtained from the six female CFS patients and six sedentary female controls who served as subjects.

CFS patients were referred for exercise testing following prescreening by their primary care physician. Only individuals with a confirmed and rigorous diagnosis of CFS according to the criteria established by Fukuda et al. (9) participated in the study. Individuals with concurrent medical disorders, or who had been treated with drugs that modulate the immune, cardiovascular, or respiratory systems within six weeks of testing were excluded from the study. Additionally, the investigators disqualified from the study patients with medical disorders that may have interfered with their ability to perform the graded exercise test. American College of Sports Medicine guidelines for contraindications

were used for prescreening and selection of control subjects. Subjects were instructed to avoid food, alcohol, and caffeine for at least three hours prior to testing. They were also asked to avoid significant exertion or exercise for 24 hours prior to testing.

The entire procedure for exercise testing was explained in detail to each study participant. Subjects were fitted with ECG electrodes for monitoring of heart rhythm and expired air was collected.

### ***Procedure***

The exercise tests comprised incremental protocols to maximal exertion. The CFS patients performed a modified Bruce treadmill protocol ( $n = 2$ ) or a 10W/min ramping protocol on a cycle ergometer ( $n = 4$ ). The control subjects performed a 20W/min ramping protocol ( $n = 6$ ) so that all of the CFS patients and controls reached maximal exertion between 9 and 13 minutes of exercise. Oxygen consumption was measured breath by breath and blood pressure was taken manually every two minutes. To ensure safety during and after the exercise bout subjects were closely monitored for adverse effects by measurement of blood pressure, oxygen saturation, cardiac rhythm, and other indicators of stress.

### ***Statistical Analysis***

Discriminant analysis was chosen to determine whether exercise performance variables of peak oxygen consumption ( $VO_{2\text{ peak}}$ ), anaerobic threshold (AT), percent of predicted heart rate (HR%) and exercise duration (DUR) could reliably differentiate between CFS patients and sedentary controls for each of two exercise tests. Preliminary correlational analyses revealed evidence of multicollinearity between the predictor variables of  $VO_{2\text{ peak}}$  and AT, test 1  $R = 0.81$ , test 2  $R = 0.88$ . To guard against potential type I errors AT was omitted from all multivariate analyses. Descriptive statistics for both tests are included in Table 1. All Statistical analyses were performed using SPSS 13.0 software for Windows operating systems.

## ***RESULTS***

During the first exercise test none of the variables qualified for discriminant analysis suggesting parity in exercise performance be-

TABLE 1. Means and standard deviations for exercise performance variables by group and test.

	Test 1		Test 2	
	CFS	Controls	CFS	Controls
VO <sub>2 peak</sub> *	26.23(4.92)	28.43(7.27)	20.47(1.80)	28.90(8.06)
AT*	15.01(4.90)	17.55(4.85)	11.01(3.43)	18.00(5.25)
HER (%)	94.83(8.86)	87.0(25.44)	87.83(9.36)	97.67(7.20)
DUR (min)	9.3(2.44)	7.78(1.98)	8.35(2.51)	8.30(1.57)

\* ml/kg/min

tween the CFS patients and the sedentary but otherwise healthy control group. For the analysis of the second exercise test stepwise discriminant analysis generated one significant function that differentiated between CFS patients and controls,  $\chi^2 = 0.32$ ,  $\chi^2 (3, N = 12) = 9.67$ ,  $p = 0.02$ . CFS diagnosis was found to account for 67.9% of function variance. Standardized function coefficients and correlation coefficients showed VO<sub>2 peak</sub> contributing most to the difference between groups (Table 2). Further univariate analyses concurred with this interpretation. For purposes of clarity AT was included in the univariate follow-up. The CFS patients were significantly lower for VO<sub>2 peak</sub>,  $F(1,10) = 6.25$ ,  $p = 0.03$ , and AT  $F(1,10) = 7.47$ ,  $p = 0.02$ . Group differences in HR% and duration did not reach significance in the univariate analyses ( $p > .05$ ). Classification results revealed that all six CFS patients and five out of six controls were correctly classified. Overall classification accuracy for the sample was 91.7%.

## DISCUSSION

The results of the first exercise test failed to differentiate between the CFS patients and controls in this study while a second exercise test, per-

TABLE 2. Correlation coefficients and standardized function coefficients.

	Correlation Coefficients with Discriminant Function	Standardized Function Coefficients
VO <sub>2 peak</sub>	.543	1.034
HER	.443	.996
DUR	-.008	.333

formed 24 hours later, produced significantly different outcomes. This finding adds credence to the idea that a single test may be insufficient to identify abnormalities in exercise performance among CFS patients. That the CFS patients could not reproduce their performance on the first test is indicative of the post-exertional malaise that may be unique to this illness (10). The control group actually improved slightly from test 1 to test 2. It is particularly telling that even the one control subject misclassified during the discriminant analysis showed improved performance between tests.

We showed in a previous study that the cardiopulmonary responses to a single bout of maximal exercise in CFS patients display wide variability, from significantly lower than expected to near normal responses (11). The wide variability in maximal oxygen consumption among our studies, and of others, lends support for the notion that variables such as detraining or illness duration may confound meaningful interpretation of the cardiopulmonary responses in CFS.

Deconditioning in CFS patients has been suggested to explain the relatively low performance of CFS patients (12). The profound reduction in physical activity that accompanies CFS symptoms certainly results in deconditioning. In isolation, the similarity of results between patients and controls for the first test in this study do not contradict a deconditioning hypothesis for CFS performance. However, the fall in oxygen consumption among the CFS patients on the second test appears to suggest metabolic dysfunction rather than a sedentary lifestyle as the cause of diminished exercise capacity in CFS.

Low exercise performance among CFS patients is sometimes discounted with allegations of poor effort or malingering on the test precipitated by an irrational fear of physical activity, or kinesiophobia (13, 10). However, all patients in the present study met criteria for maximal effort on both exercise tests. Other research has also failed to find a relationship between kinesiophobia and exercise performance in CFS (14). The criteria for maximal effort on a cardiopulmonary exercise test are especially important for appropriate interpretation of the findings from this test-retest design. ACSM provides absolute and relative indications for stopping an exercise test as well as criteria defining maximal effort (15). Accurate comparison between two exercise tests can be made only where maximal effort is given on both tests. For instance if maximal effort is not reached on the second exercise test the difference between the two tests may be due solely to the difference in effort rather than some metabolic abnormality unmasked by the response to the first test. Where maximal effort is given on both tests, a finding of reduced oxygen consumption on the second test clearly illustrates oxidative and/or metabolic dysfunction.

The mechanisms responsible for the differential responses observed in this study are not known. However, a recent study exploring the relationship between exercise performance and immune dysfunction in CFS identified a link between reduced oxygen uptake and certain immunological variables, specifically elastase and protein kinase R (PKR) activity (14). In addition to providing an explanation for the abnormal exercise performance of some CFS patients, these findings may also inform the anomalous test-retest results obtained from the present study. While the present study did not collect any measures of immune function, the results are consistent with an immune dysregulation hypothesis. The proposed role of elastase in limiting exercise performance provides a plausible explanation for the differential results obtained for CFS and controls on the second test only. There is a body of research showing that exercise stress affects immune function and the greater the stress the more significant the changes (16). It is very possible that the first test induced greater stress in the CFS patients and therefore a more extreme immune response. This may be compounded by the systemic immune deregulation proposed as an explanation for CFS pathology and the inherent low fitness levels associated with extreme sedentary behavior. In addition to immunological problems, autonomic abnormalities, neuroendocrinological dysfunction and metabolic insufficiencies may contribute to the differences between the two exercise tests in the CFS patients.

The results from cardiopulmonary exercise test-retest are highly reproducible in a number of pathologic conditions. In 114 paired tests in 42 patients with pulmonary hypertension, peak  $\text{VO}_2$  and heart rate varied by less than 7% (8). Patients with end-stage renal disease demonstrated peak  $\text{VO}_2$  variability of 4.7% (17). Variability of peak  $\text{VO}_2$  and anaerobic threshold in cardiac patients has also been shown to be less than 7% (18,19). Similarly, cystic fibrosis patients (20), and patients with obstructive pulmonary disease (21), reproduce exercise physiologic measures with very low variability. The control subjects in the present study show variability of less than 3% for peak  $\text{VO}_2$  and  $\text{VO}_2$  at anaerobic threshold. However, the reductions in these measures for the CFS patients on the second test is 22% and 26%, respectively. We believe that this difference may be a distinctive feature of the syndrome and allow differentiation between the fatigue produced by CFS and fatigue associated with other illnesses.

### CONCLUSIONS

Although the sample size was small and subjects comprised women only, this study demonstrates the potential problems associated with using single test only paradigms to assess physiological functioning in CFS. The etiology of CFS and coping strategies adopted by patients may conspire to mask the symptoms of post-exertional malaise that define this illness. Care must be taken in extrapolating too much from the exercise and immune function literature. However, the immune hypothesis for CFS does provide an explanation for the results obtained in the present study. It is further proposed that the test-retest paradigm employed here be considered as a standardized stressor for quantifying the level of impairment experienced by a CFS patient in the post-exertional state.

### REFERENCES

1. De Becker P, Roeykens J, Reynders M., McGregor N, De Meirleir K. Exercise capacity in chronic fatigue syndrome. *Arch Intern Medicine* 2000; 160(21): 3270-3277.
2. Snell CR, VanNess JM, Strayer DR, Stevens SR. Exercise and Immune Function in Male and Female Chronic Fatigue Syndrome Patients. *In Vivo* 2005; 19: 387-390.
3. Gleeson M. Biochemical and immunological markers for overtraining. *J Sports Sci Med* 2002; 1:31-41.

4. Marlin RG, Anchel H, Gibson JC, Goldberg WM, Swinton M. An evaluation of multidisciplinary intervention for chronic fatigue syndrome with long-term follow-up, and a comparison with untreated controls. *Am J Med* 1998; 28; 105(3A):110S-114S.
5. Make B, Jones JF. Impairment of patients with chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome* 1997; 3(4):43-55.
6. Edwards R, Gibson H, Clague J, Helliwell. Muscle histopathology and physiology in chronic fatigue syndrome. *Ciba Foundation Symposium* 1993; 173:102-117.
7. Weisman IM, Zeballos J. (Eds.). *Clinical exercise testing*. New York: Karger. In *Progress in Respiratory Research* 2002; Volume 32; C.T. Bolliger, Editor.
8. Hansen JE, Sun X-G, Yasunobuy, Garafano RP, Gates G, Bast RJ, Wasserman K. Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary arterial hypertension. *Chest* 2004; 126:816-824.
9. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. Chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine* 1994; 121:953-959.
10. Blackwood SK, MacHale SM, Power MJ, Goodwin GM, Lawrie SM. Effects of exercise on cognitive and motor function in chronic fatigue syndrome and depression. *J Neurol Neurosurgery and Psychiatry* 1998; 65(4):541-548.
11. VanNess, JM, Snell CR, Dempsey WL, Strayer DR, Stevens SR. Subclassifying chronic fatigue syndrome through exercise testing. *Med Sci Sports Exerc* 2003; 35(6): 908-913.
12. Nijs J, DeMeirleir K, Duquet W. Kinesiophobia in chronic fatigue syndrome: Assessment and associations with disability. *Arch Phys Med Rehab* 2004; 85(10):7.
13. Inbar O, Rotstein A, Whipp BJ. Physiological responses to incremental exercise in patients with chronic fatigue syndrome. *Med Sci Sports Exerc* 2001; 33(9):8.
14. Nijs J, McGregor NR, Meeusen R, deSchutter G, vanHoof E, deMeirleir K. Chronic fatigue syndrome: exercise performance related to immune dysfunction. *Med Sci Sports Exerc* 2005; 37(10):8.
15. American College of Sports Medicine ACSM's Guidelines for Exercise Testing and Prescription 6th Edition 2000. Philadelphia, PA: Lippincott, Williams and Wilkins.
16. Petersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration and adaptation. *Physiological Reviews* 2000; 80(3): 1055-1081.
17. Koufaki P, Naish PF, Mercer TH. Reproducibility of exercise tolerance in patients with end-stage renal disease. *Arch Phys Med Rehabil*, 2001; 82:1421-1424.
18. Lehman G, Kolling K. Reproducibility of cardiopulmonary exercise parameters in patients with valvular heart disease. *Chest* 1996; 110:685-692.
19. Janicki JS, Gupta S, Ferris ST, McElroy PA. Long term reproducibility of respiratory gas exchange measurements during exercise in patients with stable cardiac failure. *Chest* 1990; 97:12-17.
20. McKone EF, Barry SC, FitzGerald MX, Gallagher CG. Reproducibility of maximal exercise ergometer testing in patients with cystic fibrosis. *Chest* 1999; 116: 363-368.
21. Marciniuk DD, Watts RE, Gallagher CG. Reproducibility of incremental maximal cycle ergometer testing in patients with restrictive lung disease. *Thorax* 1993; 48:894-898.