Exercise Tolerance Testing in a Prospective Cohort of Adolescents with Chronic Fatigue Syndrome and Recovered Controls Following Infectious Mononucleosis

Ben Z. Katz, MD[1]

Steven Boas, MD[1]

Yukiko Shiraishi, PhD[2]

Cynthia J. Mears, DO[1]

Renee Taylor, PhD[2]

From the Department of Pediatrics, Northwestern University, Feinberg School of Medicine and Children's Memorial Hospital[1], and the Department of Occupational Health, College of Applied Sciences, University of Illinois at Chicago[2].

Supported by R01HD4330101A1 from the National Institute of Child Health and Human Development.

Corresponding author: Ben Z. Katz, MD, Children's Memorial Hospital, Division of Infectious Diseases, 2300 Children's Plaza, Box # 20, Chicago, IL 60614, Tel: 773-880-8226, Fax: 773-880-8226, e-mail: bkatz@northwestern.edu

Short title/Running head:

There are no conflicts of interest to report.

Keywords: adolescent health, chronic fatigue syndrome, infectious mononucleosis, exercise tolerance

Abstract

Background: Chronic fatigue syndrome (CFS) is a complex and controversial condition responsible for marked functional impairment. We recently reported that six months following acute infectious mononucleosis (IM), 13%, of adolescents met criteria for CFS.

Objective: To measure exercise tolerance in adolescents with CFS and controls 6 months following IM.

Design/Methods: 21 adolescents diagnosed with CFS 6 months following IM and 24 controls who had completely recovered from IM 6 months prior performed a maximal incremental exercise tolerance test with breath by breath gas analysis. Salivary cortisol was measured before and after exercise. All values are expressed as mean $\pm$ standard deviation.

Results: The CFS-diagnosed adolescents and controls did not differ significantly in age, weight or body-mass index (BMI). Lower VO_2 peak percent of predicted was seen in adolescents with CFS following IM compared with controls (CFS 99.3 $\pm$ 16.6 vs control 110.7 $\pm$ 19.9, $p = 0.05$). Peak oxygen pulse was also significantly lower in adolescents with CFS as compared with the recovered controls (CFS 12.4 $\pm$ 2.9 vs Controls 14.9 $\pm$ 4.3, $p = 0.03$). The lower VO_2 and peak oxygen pulse suggest a lower degree of fitness and a decreased efficiency of exercise, respectively, in adolescents with CFS compared to controls. A trend towards a greater rise in salivary cortisol levels in response to exercise was also seen in controls compared with cases.

Conclusions: Adolescents who meet the criteria for CFS 6 months following IM have a lower degree of fitness (VO_2) and efficiency of exercise (peak oxygen pulse) than

recovered adolescents. Whether these abnormal exercise findings are a cause or effect of CFS or whether they can be used to determine objectively which adolescents following IM will develop CFS remains to be determined. Nevertheless, our data demonstrate that IM produces both fatigue and measurable changes in exercise testing in a subset of adolescents.

Introduction

Chronic fatigue syndrome (CFS) is a complex and controversial condition involving severe fatigue and disabling musculoskeletal and cognitive symptoms (1). Chronic fatigue accounts for marked functional impairment and educational disruption among adolescents (2-5). We recently reported the results of a 2 year prospective study of CFS following monospot-positive acute infectious mononucleosis (IM) in adolescents. Six months following IM, 13%, of adolescents met criteria for CFS (6). As part of their 6 month evaluation, 21 adolescents diagnosed with CFS and 21 controls who were completely recovered from their IM participated in an exercise tolerance test; salivary cortisol was also measured before and after exercise. Herein we report the results of that testing.

Methods

We enrolled adolescents in the greater Chicago area with monospot-positive acute IM, identified via school nurses, pediatric practices, including the Pediatric Practice Research Group (7) and the Virology Laboratory of Children's Memorial Hospital. Six months following their IM diagnosis, a telephone screening interview identified those not fully recovered and 50 recovered controls willing to come for a clinical evaluation. All aspects of the study were approved by the Institutional Review Boards of Children's Memorial Research Center and the College of Applied Sciences of the University of Illinois at Chicago.

Definitions. We used the Jason et al. (8) revision of the Fukuda (1) criteria to diagnose CFS. When a well-recognized underlying condition, such as primary depression, could explain the subject's symptoms, we classified him/her as having "CFS-explained".

Evaluation. The 6 month clinical evaluation consisted of a complete history, physical examination and laboratory screening to rule out medical causes of CFS (e.g., urine toxicology and thyroid function tests). Using the data from the clinical evaluation, a diagnosis of CFS, CFS-explained, or recovered was made on each subject after review by an expert panel. A subset of CFS case patients and controls participated in an exercise tolerance test. Participants' saliva was collected 10 minutes before, immediately after, and 60 minutes after the exercise tolerance test to measure (changes in) cortisol, a known stress response to exercise.

Anthropometric measures and body composition. Stature was measured using a stadiometer and weight was obtained using a platform beam scale. Body mass index

(BMI) was calculated as weight/height (kg·m-2). Fat free mass (FFM, a measure of nutritional status) was determined using bioelectrical impedance analysis (RJL Systems, Clinton Twp, MI) to evaluate the subjects overall nutritional status (lean body mass, percent of lean muscle) per manufacturer's instructions.

Static pulmonary function testing. Spirometry (SensorMedics Inc., Yorba Linda, CA) was performed according to American Thoracic Society Standards before the exercise test to measure FEV_1, with values expressed as a percent of predicted for height, weight, and age (9,10).

Dynamic pulmonary function testing. All study subjects were asked to refrain from strenuous activity one day before testing at the Pulmonary Exercise Laboratory. All subjects performed a graded maximal exercise test on an electronically braked cycle ergometer (Lode Excalibur, Groningen, Netherland) per the Godfrey protocol (11). Subjects maintained a cadence of 60 revolutions per minute throughout the test. Incremental increases in work load were made each minute based on the child's stature: 10, 15, and 20 W for those shorter than 1.2 meters, 1.2–1.4 meters, and taller than 1.4 meters, respectively. Peak work capacity (exercise tolerance) was determined as the last work load at which the patient pedaled for a full minute. Oxygen consumption (VO_2) was determined (VMax 229,SensorMedics Inc., Yorba Linda, CA) and recorded every 30 sec. Oxyhemoglobin saturation (SaO2) was monitored continuously via pulse oximetry (Nellcor, Hayward, CA) throughout the test. A test was considered maximal if the heart rate exceeded 90% of predicted maximal values, a plateau occurred in oxygen consumption that did not rise with increasing work load, or if the oxyhemoglobin

saturation dropped more than 5% from baseline (12). Verbal encouragement was given throughout the test.

The following data were collected: Work slope (Δ VO2/ Δ Work Capacity, i.e., the change in oxygen consumption divided by work capacity), minute ventilation (liters of air moved per minute) at peak work capacity, breathing reserves (as indicated by minute ventilation / Maximal Voluntary Ventilation [MVV, the theoretical amount of O_2 one can breathe in] or by MVV – minute ventilation), respiratory quotient (the ratio of CO_2 produced to O_2 consumed), the peak O_2 pulse (oxygen consumption per heartbeat) and ventilatory equivalents (VE/VCO2 and VE/VO2; the ratio of air breathed per minute related to carbon dioxide or oxygen respectively).

Technicians administering the exercise testing and the Pulmonologist (SB) interpreting the testing were blinded as to the patients' diagnosis (CFS vs. recovered control).

Analysis. Chi square tests were used to evaluate the significance of categorical data. T-tests (two-tailed) or Kruskal Wallis tests, as appropriate, were used to evaluate continuous data.

Results

There were 301 adolescents with monospot-positive infectious mononucleosis enrolled in the study. Six months following their IM diagnosis, 286 (95%) completed a telephone screening interview. Based on the screening interview, 70 of these adolescents (24%) were assessed as not fully recovered. A 6 month clinical evaluation was completed on 53 (76%) of these 70 not fully recovered adolescents, following which 39 of the 53 were classified as having CFS (13% of the original sample of 301 adolescents). Thirty-five of the 39 subjects with CFS at 6 months were female (90%), and all were at least Tanner stage 4 (6).

Fifty adolescents who had fully recovered from IM and who were willing to enter a clinical trial underwent the same 6 month evaluation, and comprised the control population. There was no difference in age, race and socioeconomic status between recovered adolescents who were and were not used as controls for this study (6, and data not shown).

Subject Characteristics

Twenty-one of the 39 adolescents diagnosed with CFS at 6 months and 21 of 50 fully recovered controls participated in the exercise tolerance test. The 21 CFS patients consisted of 18 females and 3 males. The 21 recovered controls also consisted of 18 females and 3 males. There was no difference between the cases and controls who did and did not undergo exercise testing in several parameters examined (age, sex, socio-economic status, body mass index and modifiable activity questionnaire responses; data not shown).

Baseline physical characteristics of CFS patients and recovered controls are summarized in Table 1. No significant differences were seen in age, sex, stature, weight or body mass whether expressed in absolute terms or as percentiles. No differences were seen in body mass index or body fat percent. Only 1 patient with CFS and one recovered control had a BMI > 30. None of our subjects were obese. Baseline spirometry indicated no significant difference in the FEV_1 between groups. Baseline oxyhemoglobin saturations were also similar between the 2 groups.

Exercise Parameters

Exercise Tolerance. Peak work capacity (a global indicator of exercise tolerance), whether expressed as absolute or percent predicted, was similar for both the CFS and recovered control groups. However, oxygen consumption was significantly higher in the control group, whether expressed in absolute terms (2.75 ± 0.75 vs 2.32 ± 0.57 l/min, p=0.04) or as a percent of predicted (110.7 ± 19.9 vs 99.3 ± 16.6%, p=0.05), as was the work slope ($\Delta VO_2/\Delta$ work capacity) (12.31 ± 1.69 vs 10.9 ± 1.3, p=0.005), indicating that subjects with CFS had a lower degree of fitness than the recovered controls.

Ventilatory Response. Both the respiratory rate and minute ventilation at peak exercise did not differ between groups. Breathing reserves were similar. Ventilatory Equivalents for both oxygen and carbon dioxide did not differ, nor did the $\Delta VE/\Delta VCO_2$ ratio.

Gas Exchange. Neither the respiratory quotient nor the peak end tidal CO_2 differed between subjects with CFS and recovered controls. Peak oxyhemoglobin saturations were statistically significantly higher in the CFS group (96.1 ± 1.3 vs 95.2 ± 1.6%, p=0.02), although the biological significance of these differences is unclear.

Cardiovascular Response. Peak heart rate was similar in both groups. Peak oxygen pulse was significantly higher in the recovered controls whether expressed in absolute terms (14.9 ± 4.3 vs 12.4 ± 2.9, p=0.03) or relative to percent predicted (114.1 ± 17.9 vs 103.3 ± 16.6%, p=0.05), implying that recovered controls exercised more efficiently than subjects with CFS. Table 2 summarizes the exercise testing data.

Salivary Cortisol Response to Exercise

The Kruskal Wallis Test was used to examine the pattern of cortisol change in response to exercise in adolescents with CFS and recovered controls. Relative change from baseline (T1) to immediately after maximal oxygen consumption (VO_2 max) (T2), and immediately after (T2) to 60 minutes after exercise (T3) were compared between cases and controls. Though there seemed to be a greater rise in salivary cortisol levels in response to exercise in recovered controls (51% increases) compared with cases with CFS (7% increase), this was not statistically significant. A sluggish cortisol response in subjects with CFS would also be consistent with subjects with CFS exercising less efficiently than recovered controls. See Table 3.

Discussion

There have been 11 previous reports of exercise testing in adults with CFS which included comparison (control) groups. These studies differed in terms of the control groups examined (e.g., normal vs. sedentary), whether the sickest CFS patients were excluded, whether the patients were encouraged to exercise to maximum capacity, and whether only females or both sexes were studied. Predictably, results varied as well, with the majority showing decreased exercise capacity and fitness levels in subjects with CFS, and inconsistent data regarding heart rate responses to exercise (13-23). A single, uncontrolled pediatric study demonstrated that maximal exercise capacity was reduced in 5-30% of subjects with CFS (24).

Because there were no previous controlled pediatric trials, we undertook to prospectively examine exercise testing in our cohort of adolescents with CFS and recovered controls. We examined both absolute and percent predicted work capacity and neither were statistically significantly different between our recovered controls and the patients with CFS. However, oxygen consumption, work slope and peak oxygen pulse were significantly higher in recovered controls than in patients who met the criteria for CFS 6 months following IM, indicating a lower degree of fitness in CFS cases 6 mos. following IM vs. recovered controls. Because we saw no abnormalities related to the efficiency of breathing, baseline lung function or peak work capacity, while we did see a greater rise in salivary cortisol in response to exercise in subjects with CFS, the lower degree of fitness we saw in our CFS cohort may be related to subtle regulatory abnormalities of cardiac function. These data are also consistent with recent data we have reported regarding orthostatic intolerance in subjects with CFS when compared with

recovered controls (25). Future analyses will examine autonomic symptoms, fatigue scores, cytokine responses, gene array and psychiatric data that were prospectively collected on our subjects.

Acknowledgements

We thank the Pediatric Practice Research Group (7) and all of the physicians and school nurses who referred patients into our study:

Physicians:

Bedingfield and Rosewell, S.C*.; Dr. Dianna Brogan - Associated Pediatricians*; Dr. Linda Hamilton - Pediatric Health Associates*; Dr. Paul Goldstein - Pediatric Health Care Associates*; Dr. Peter Liber - Wheaton Pediatrics*; Dr. Rayner- Advocate Health Centers*; Dr. Rosa Choi-Pediatrics Unlimited, S.C.*; Dr. Tony Sallamme - Near North Health Service Corporation Komed/Holman Health Center*; Dupage Pediatrics*; Evanston Northwestern Health Care*; FGM Pediatrics*; Lake Forest Pediatric Associates, Ltd.*; Medical Pediatrics Limited*; Dr. Edward Traisman-Traisman, Benuck, Traisman & Merens*; Children's Memorial Hospital*; Columbia College Student Health Center; Dr. Elizabeth Becerra - Centro Medico; Dr. Howard Rice - Town and Country Pediatrics; Dr. Jason Canel - Glenview Primary Care-Pediatrics; Dr. Jean Kim - Lutheran General; Dr. Klaus - Pedios Medical Center; Dr. Lenore Sue - Wheaton Medical; Dr. Margaret Thompson - Well Group Health Partners; Dr. Martine Nelson; Dr. Marvin Cooper - North Shore Pediatrics Associates; Dr. Minal Giri; Dr. Oscar Novick; Dr. Patrick Tranmer - UIC Pediatrics/Family Practice; Dr. Paul Panzika; Dr. Ronald Cohn - Advocate Medical Group; Dr. Ruby Roy - Loyola Medical Center; Dr. Sana Attar; Dreyer Medical Group; Mundelein Pediatrics; Rush Pediatric Primary Care Center

School Nurses:

Arlette Johnson - Waukegan High School; Barbara Sibley - Prospect High School; Beth Hirsch - Sycamore Senior High School; Cameron Traut - Libertyville Middle School; Carol Fitzhenry - Niles North High School; Carol Menses - Fenton High School; Debbie Lawrence - Lincoln Way East High School; Debbie Spagnola - William Harvard Taft High School; Donna Schaffer - Benet Academy; Donna Zenger - Chippewa Middle School; Jackie Forst - Glenbrook North High School; Jean Karris - Glenbrook South High School; Jeanne Grey - Attea Middle School; Joanne Bratta - Rolling Meadows High School; Joanne Monahan, Colleen Conley, Tallya Knippen - Wheaton Warrenville South High School; Judy Smith - Naperville Central High School; Kathryn Hunter - Carmel Catholic High School; Kathy Marthaler - Glenbard West High School; Kathy Olsen - Barrington High School; Kathy Sczepanski - Elk Grove Village High School; Kathy Sophie - Barrington Middle School-Station Campus; Kathy Tomassi - Main South High School; Laura Mauressi - St. Ignatius College Prep; Linda Wahlstrom - DeKalb High School; Lori Meska - Wheeling High School; Lori Michaels - Lake Zurich High School; Lucy Brinka - Lake Park West High School; Margaret Olsen - Glenbard North High School; Marie Walters - Elgin High School; Marie Walters - South Elgin High School; Marilyn Colby - Deerfield High School; Martha Manno - Cary Grove Community High School; Mary Ellen Sjostrom - Oak Park River Forest High School; Mary Jane Chiado - Mundelein High School; Mary Jo Canalli - Larkin High School; Mary Kolaritis - Batavia High School; Mary McConald - Lake Park East High School; Mrs. Fontanarosa, Mrs. Perkins, and Mrs. Knippen - Edison Middle School; Mrs. Patterson - Highland Middle School;

Ms. Boynton and Ms. Voneregó - St. Charles North High School; Nancy Boros - St. Scholastica Academy; Nancy Wallbear - Hubbard High School/ Oak Grove Elementary School; Nena Miller - Homewood Flossmoor High School; Pamela Bertolani - Willowbrook High School; Pamela Seubold - Naperville North High School; Pat Hatz - York High School; Peggy Bassrawi - Niles West High School; Ronnie Alshouse - Grayslake High School; Sandra Frued - Glenbard East High School; Stacy Wodka - Buffalo Grove High School; Susan Theisen - Wheaton North High School

References

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff, A. The Chronic Fatigue Syndrome: A comprehensive approach to its definition and study. Ann Intern Med 1994;121:953-959.

2. Marshall GS, Gesser RM, Yamanish, K, Starr SE. Chronic fatigue in children: Clinical features, Epstein-Barr virus and human herpes virus 6 serology and long term follow-up. Pediatr Infect Dis J 1991;10:287-290.

3. Richards J, Turk J, White S. Children and adolescents with chronic fatigue syndrome in non-specialist settings: Beliefs, functional impairment and psychiatric disturbance. Eur Child Adolesc Psychiatry 2005;14:310-318.

4. Sankey A, Hill CM, Brown J, Quinn L, Fletcher A. A follow-up study of chronic fatigue syndrome in children and adolescents: Symptom persistence and school absenteeism. Clin Child Psychol Psychiatry 2006; 11: 126-138.

5. ter Wolbeek M, van Doornen LJ, Kavelaars A, Heijnen CJ. Severe fatigue in adolescents: A common phenomenon? Pediatrics 2006; 117(6): e1078-86.

6. Katz BZ, Shiraishi Y, Mears CJ, Binns HJ, Taylor R. Chronic fatigue syndrome following infectious mononucleosis in adolescents. Pediatrics 2009;124:189-93. http://www.pediatrics.org/cgi/content/full/124/1/189 doi:10.1542/peds.2008-1879

7. LeBailly S, Ariza A, Bayldon B, Binns HJ; for the Pediatric Practice Research Group. The origin and evolution of a regional pediatric practice-based research network: Practical and methodological lessons from the Pediatric Practice Research Group. Curr Probl Pediatr Adolesc Health Care 2003;33:124-134.

8. Jason LA, Jordan K, Miike T, et al. A pediatric case definition for myalgic encephalomyelitis and chronic fatigue syndrome. J Chronic Fatigue Syndr 2006;13:1-44.

9. American Thoracic Society/European Respiratory Society, ATS/ESR Task Force. Standardization of lung function testing : General considerations for lung function testing. Eur Respir J 2005 ;26 :153-61, 319-38, and 511-22.

10. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med 1999 ;159 :179-87.

11. Godfrey S. Exercise Testing in Children. London: W.B. Saunders. 1974.

12. Rowland TW. Aerobic exercise testing protocols. IN: Rowland TW, ed. Pediatric Laboratory Exercise Testing: Clinical guidelines. Human Kinetics Publishers. Springfield, MA. 1993. pp. 32-4.

13. Riley MS, O'Brien CJ, McCluskey DR, Bell NP, Nicholls DP. Aerobic work capacity in patients with chronic fatigue syndrome. BMJ 1990;301:387-9.

14. Sisto SA, LaManca J, Cordero DL, et al. Metabolic and cardiovascular effects of a progressive exercise test in patients with chronic fatigue syndrome. Am J Med 1996;100:634-40.

15. Fulcher KY, White PD. Strength and physiological response to exercise in patients with chronic fatigue syndrome. J Neurol Neurosurg Psychiatry 2000;69:302-7.

16. De Becker P, Roeykens J, Reynders M, McGregor N, De Meirleir K. Exercise capacity in chronic fatigue syndrome. Arch Intern Med 2000;160:3270-7.

17. Inbar O, Dlin R, Rotstein A, Whipp BJ. Physiologic responses to incremental exercise in patients with chronic fatigue syndrome. Med Sci Sports Exerc 2001;33:1463-70.

18. Bazelmans E, Bleijenberg G, van der Meer JWM, Folgering H. Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? Psycholog Med 2001;31:107-14.

19. Sargent C,Scroop GC, Nemeth PM, Burnet RB, Buckley JD. Maximal oxygen uptake an dlactate metabolism are normal in chronic fatigue syndrome. Med Sci Sports Exerc 2002;34:51-6.

20. Cook DB, Nagelkirk PR, Peckerman A, Poluri A, Lamanca JJ, Natelson BH. Perceived exertion in fatiguing illness. Med Sci Sports Exerc 2003;35:563-8.

21. Georgiades E, Behan WMH, Kilduff LP, et al. Chronic fatigue syndrome: new evidence for a central fatigue disorder. Cli Sci 2003;105:213-8.

22. Wallman KE, MortonAR, Goodman C, Grove R. Physiologic response during a submaximal cycle test in chronic fatigue syndrome. Med Sci Sports Exerc 2004;36:1682-8.

23. Gallagher AM, Coldrick AR, Hedge B, Weir WRC, White PD. Is the chronic fatigue syndrome an exercise phobia? J Psychosom Res 2005;58:367-73.

24. Takken T, Henneken T, van de Putte E, Helders P, Engelbert R. Exercise testing in children and adolescents with chronic fatigue syndrome. Int J Sports Med 2007;28:580-4.

25. Katz BZ, Stewart J, Shiraishi Y, Mears CJ, Taylor R. Orthostatic tolerance testing in a prospective cohort of adolescents with chronic fatigue syndrome and recovered controls following infectious mononucleosis. Abstract submitted to the 2010 PAS Meeting.