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

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Abstract

Objective—Six months following acute infectious mononucleosis (IM), 13%, of adolescents meet criteria for chronic fatigue syndrome (CFS). We measured exercise tolerance in adolescents with CFS and controls 6 months following IM.

Study design—21 adolescents with CFS 6 months following IM and 21 recovered controls performed a maximal incremental exercise tolerance test with breath-by-breath gas analysis. Values expressed are mean ± standard deviation.

Results—The adolescents diagnosed with CFS and controls did not differ in age, weight, body-mass index or peak work capacity. Lower VO_2 (oxygen consumption) peak percent of predicted was seen in adolescents with CFS compared with controls (CFS 99.3 ± 16.6 vs control 110.7 ± 19.9, p = 0.05). Peak oxygen pulse also was lower in adolescents with CFS compared with recovered controls (CFS 12.4 ± 2.9 vs controls 14.9 ± 4.3, p = 0.03).

Conclusions—Adolescents with CFS 6 months following IM have a lower degree of fitness and efficiency of exercise than recovered adolescents. Whether these abnormal exercise findings are a cause or effect of CFS is unknown. IM can lead to both fatigue and measurable changes in exercise testing in a subset of adolescents.

Keywords

adolescent health; chronic fatigue syndrome; infectious mononucleosis; exercise tolerance

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

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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 also was measured before and after exercise.

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.

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."

The 6-month clinical evaluation consisted of a complete history, physical examination and laboratory screening to rule out medical causes of CFS. Routine laboratory screening for each trial participant included urianlysis and urine toxicology, urine pregnancy testing and serum estradiol (females only), complete blood count with differential, eryhthrocyte sedimentation rate, measurements of thyroid and adrenocorticotropic hormones, serum electrolytes, liver chemistries and an HIV antibody test. Using the data from the clinical evaluation, a diagnosis of CFS, CFS-explained, or recovered was made for each subject after review by an expert panel. All CFS case patients and recovered controls were offered an exercise tolerance test; those who agreed to undergo this testing were included in our analysis. As part of the exercise tolerance test, participants' saliva was collected 10 minutes before, immediately after, and 60 minutes later to measure (changes in) cortisol, a known stress response to exercise.

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.

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).

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; 12 refused, 3 had exclusionary diagnoses and 2 did not meet study criteria; there were no significant differences in sex, family socioeconomic status or subject age between groups that completed the 6-month evaluation, who refused or who were was excluded (data not shown). Following the 6-month evaluation, 39 of the 53 adolescents were classified as having CFS (13% of the original sample of 301). 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 (data not shown).

Subject Characteristics

Twenty-one of the 39 adolescents diagnosed with CFS at 6 months and 21 of 50 fully recovered controls chose to participate 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, socioeconomic status, body mass index and modifiable activity questionnaire responses; data not shown). Eighteen of the 21 adolescents with CFS and 17 of the 21 recovered controls completed their exercise testing within 1 month of their 6 month clinic visit; all subjects completed exercise testing within 50 days of their 6-month evaluation.

Baseline physical characteristics of patients with CFS and recovered controls are summarized in Table I. 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 was obese. Baseline spirometry indicated no significant difference in the

FEV_1 between groups. Baseline oxyhemoglobin saturations and heart rate were similar between the 2 groups.

Exercise Meaurements

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 II 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 also is consistent with subjects with CFS exercising less efficiently than recovered controls (Table III).

Discussion

There have been 11 previous reports of exercise testing in adults with CFS that included comparison (control) groups. These studies differed in terms of the control groups examined (e.g., normal vs. sedentary), whether the sickest patients with CFS 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, but 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. Neither absolute nor percent predicted work capacity was statistically significantly different between recovered controls and 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 months following IM vs. recovered controls. The 11% difference in peak oxygen consumption between adolescents with CFS and recovered controls is likely clinically meaningful, as 10-25% increases in VO_2 max are seen following aerobic training in normal individuals (25).

Because there were 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. We do not believe that there was a difference in conditioning between the two groups because both baseline resting heart rate and peak hear rate were similar between the two groups.

In several studies, 60-75% of adolescents who meet the criteria for CFS can date the onset of their symptoms to a specific, systemic febrile illness (26-28). Mononucleosis is a well known precipitating factor for CFS in both adults and adolescents, as are influenza and Q fever, among others, leading some to prefer the term post-infective fatigue (6,29,30). Thus it is unlikely that the exercise findings we described are specific for CFS following IM, rather that IM was the most common serious systemic infection seen in the otherwise healthy adolescents who made up our cohort.

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Table 1

Baseline characteristics of participants

	CFS	Control	P value
	N=21	**N=21**	
Age (yr), Range	17.1 (14.5 – 19.6)	17.2 (13.8 – 19.2)	.88
Sex (F:M)	(18:3)	(18:3)	
Mass (kg)	62.4 ± 10.4	66.9 ± 13.8	.25
Mass (% ile)	49.2 ± 27.4	55.1 ± 30.4	.5
Height (m)	$1.7_{[H1]}$ ± 7.2	1.7 ± 8.2	.23
Height (% ile)	50.0 ± 14.8	51.7 ± 17.2	.75
BMI (m/kg2)	22.8 ± 3.4	23.5 ± 4.5	.53
Body Fat (%)	26.4 ± 8.3	26.0 ± 10.8	.9
Static Lung Function			
FEV1 (l)	3.2 ± 0.6	3.6 ± 0.6	.13
SpO2, %	97.5 ± 1.1	97.5 ± 0.8	1.0
Cardiac Response			
HR baseline, bpm	76.4 + 11.7	74.8 + 12.9	.6

Table II

Results of exercise testing of participants

	CFS	Control	*P* value
Tolerance			
Peak work capacity, Watts	185.4 ± 37.1	201.6 ± 50.5	.24
Peak work capacity (% predicted)	115.2 ± 14.7	116.5 ± 16.7	.78
VO_2 Peak (L/min)	2.3 ± 0.6	2.8 ± 0.8	.04
VO_2 Peak (mL/kg)	37.4 ± 8.4	41.7 ± 10.7	.16
VO_2 Peak, % predicted	99.3 ± 16.6	110.7 ± 19.9	.05
Work slope	10.9 ± 1.3	12.3 ± 1.7	.005
Ventilatory parameters			
RR max	50.8 ± 9.2	52.5 ± 9.4	.55
VE max	89.2 ± 20.1	101.9 ± 29.9	.11
VE/MW	78.2 ± 14.4	80.4 ± 12.8	.61
Breathing reserve	25.8 ± 18.1	24.0 ± 16.9	.74
VE/CO_2 AT	31.1 ± 4.6	29.2 ± 3.4	.14
VE/O_2 AT	32.5 ± 4.9	30.5 ± 3.9	.14
$\Delta VE/\Delta VCO_2$	27.3 ± 4.3	26.3 ± 3.4	.39
Gas exchange			
RQ peak	1.3 ± 0.1	1.2 ± 0.1	.16
Peak $ETCO_2$	38.5 ± 4.9	37.9 ± 4.8	.66
Peak SpO2, %	96.1 ± 1.3	95.1 ± 1.6	.02
Cardiac response			
HR peak, bpm	187.6 ± 9.4	185.6 ± 11.1	.53
Peak O_2 Pulse	12.4 ± 2.9	14.9 ± 4.3	.03
Peak O2 Pulse, % predicted	103.3 ± 16.6	114.1 ± 17.9	.05

Table 3

Relationship between exercise and cortisol response

TABLE 3	**CFS**	**Control**	**P value**
Cortisol Values Mean ± SD			
T1, 10 minutes prior	0.8 ± 0.5 ng/ml	0.9 ± 0.9 ng/ml	.67
T2, Immediately post	0.8 ± 0.5 ng/ml	1.0 ± 0.9 ng/ml	.39
T3, 60 minutes post	1.2 ± 1.6 ng/ml	1.3 ± 1.0 ng/ml	.78
Percent Change			
T1 vs T2	8.7 ± 56.1	50.5 ± 137.3	.21
T2 vs T3	155.1 ± 575.3	126.0 ± 279.7	.84