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Exercise Testing in Children and Adolescents with Chronic Fatigue Syndrome

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Key words
- chronic fatigue syndrome
- children
- exercise capacity
- blood pressure

Abstract

The objective of this study was to evaluate exercise capacity in children and adolescents diagnosed with Chronic Fatigue Syndrome (CFS). We examined 20 patients (12 girls and 8 boys; mean age 14.9 ± 3.7 years) diagnosed with CFS. Exercise capacity was measured using a maximal exercise test on a bicycle ergometer and an expired gas analysis system. Fatigue was assessed using a questionnaire and a daily activity diary was used to describe activities for three days. Z-scores were calculated using age- and sex-matched reference values. Z-scores in children and adolescents with CFS were − 0.33 ± 1.0 ($p = 0.17$) for peak oxygen uptake, − 1.13 ± 1.41 ($p = 0.002$) for relative peak oxygen uptake [ml/kg/min] and − 0.93 ± 1.29 ($p = 0.07$) for maximal work load. Both heart rate and blood pressure at peak performance were significantly reduced compared to reference values. Fatigue levels were significantly positively associated with age and negatively with blood pressure at peak exercise ($p < 0.05$). In conclusion maximum exercise testing was feasible in young people with CFS. Maximal exercise capacity was only reduced in a minority of the patients and was related to current physical activity levels.

Introduction

Chronic Fatigue Syndrome (CFS) is characterized by debilitating fatigue, diminished physical and mental functioning lasting by definition at least six months [13]. Other symptoms may be present, particularly myalgia, arthralgia, mood and sleep disturbances. Hypotheses concerning the cause of CFS have ranged from persistent infection with viral or other agents to a primary psychiatric disorder. Despite all scientific efforts, however, a plausible cause for the chronic fatigue syndrome has not yet been established.

The hypoactive lifestyle of patients with CFS [35] has led to the suggestion that a reduction in exercise capacity might contribute to their perceived fatigue [12,25] and prolongs their illness. The notion of reduced exercise capacity is supported by most previous exercise studies in adults with CFS, which describe reductions in peak oxygen uptake ($\dot{V}O_{2peak}$) [5,11,12,14,31], peak work load [12,40], reductions in peak heart rate [14,31], and earlier exhaustion [12,14,25,31]. These findings, however, were not confirmed in all studies [4,30]. Discrepancies between studies might be explained by differences in characteristics of included patients and healthy controls (i.e. disease duration and physical activity levels). The majority of studies concerning CFS have concentrated on the adult population; children and adolescents have received much less attention. The very essence of diagnosis and the clinical labeling of such children has even been questioned [17]. Despite this, there has been recent widespread concern about the apparent increase of CFS in the pediatric population [1]. The impact of CFS is profound and responsible for frequent and long-term absences from school [37] since as many as 44 percent of adolescents remain ill with significant symptoms, as observed in an eight year follow-up study [15].

The objectives of this study were to investigate whether maximal exercise testing is feasible in children and adolescents with CFS and to evaluate whether exercise capacity is impaired in subjects with childhood CFS. We also investigated whether exercise parameters are related to fatigue levels in children and adolescents with CFS.

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Materials and Methods

Population

We examined 20 patients (12 girls and 8 boys; mean age 14.9 ± 3.7 years) diagnosed with CFS. The mean (± SD) duration of symptoms was 2.4 ± 1.6 years. These patients were referred to a special CFS outpatient clinic of the Wilhelmina Children's Hospital Utrecht between May and October 2004. All patients were Caucasian and fulfilled the Center for Disease Control and Prevention (CDC) criteria for chronic fatigue syndrome [13] at the time of inclusion. All patients were diagnosed by the same pediatrician (EMP). Patients and parents were fully informed about the test procedures and the possible risks involved and informed consent was obtained. All procedures were approved by the Medical Ethics Committee of the University Medical Center Utrecht.

Anthropometry

Body height and weight were measured without shoes and heavy clothing, to the nearest cm and 100 g, respectively. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of body height in meters. Subcutaneous adiposity was measured from skin fold measurements using Harpenden skinfold calipers. The measurements were taken at 7 sites at the right site of the body; triceps, biceps, subscapular, suprailiacal, mid-abdominal, medial calf and thigh by the test leader and in accordance with the American College of Sports Medicine guidelines [18]. The sum of the 7 skin folds was used as an index for subcutaneous adiposity after Pollack et al. [24].

Cardiopulmonary exercise test and blood pressure monitoring

Subjects performed a maximal exercise test using an electronically-braked cycle ergometer (Lode Examiner, Lode BV, Groningen, The Netherlands). Patients started to cycle at 0 Watt for 1 minute. Thereafter work rate was increased 20 Watt per minute to bring the patient to his or her limit between 8 and 12 minutes of exercise [8]. This protocol continued until the patient stopped because of volitional exhaustion, despite standardized verbal encouragement of the investigators. During the maximal exercise test, subjects breathed into a facemask (Hans Rudolph Inc, Kansas City, MO, USA) connected to a calibrated expired gas analysis system (Oxycon Champion, Viasys Bilthoven, the Netherlands). Expired gas was passed through a flow meter, an oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzers were connected to a computer, which calculated breath-by-breath minute ventilation, oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and respiratory exchange ratio (RER = $\dot{V}CO_2/\dot{V}O_2$). During the maximal exercise test, heart rate (HR) was monitored continuously by a three-lead electrocardiogram (Hewlett-Packard, Amstelveen, The Netherlands), and transcutaneous oxygen saturation (SaO_2) by pulse oximetry (Nellcor 200 E, Breda, The Netherlands). $\dot{V}O_2$ plateau was defined as a change < 8 mL · min^{-1} · Watt^{-1} in $\dot{V}O_{2peak}$ during the final work stage of the test [10]. Absolute peak oxygen uptake ($\dot{V}O_{2peak}$) was taken as the average value over the last 30 seconds during the maximal exercise test. W_{peak} was the highest achieved workload. Relative $\dot{V}O_{2peak}$ ($\dot{V}O_{2peak/kg}$) was calculated as absolute $\dot{V}O_{2peak}$ divided by body mass. Predicted $\dot{V}O_{2peak}$ and W_{peak} values were obtained from established values from age- and sex-matched Dutch controls [6]. The reference values are obtained in a population of 336 healthy Dutch children and adolescents (158 boys and 178 girls) in the age between 4 and 18 years [6].
Systolic and diastolic blood pressure were measured in an upright sitting position using an automatic device (Dynamap 1846 SX, Critikon Inc, Tampa, FL, USA) at the start (after 5 minutes rest), and at the end of exercise.

Checklist individual strength (CIS-20)

The CIS-20 is a reliable and validated questionnaire and consists of 20 questions [36]. In this questionnaire the patient is asked about fatigue in the two weeks preceding the assessment. It is designed to measure four aspects of fatigue, namely subjective experience of fatigue (eight items, e.g., "I feel tired"), concentration (five items, e.g., "I have trouble concentrating"), motivation (four items, e.g., "I feel no desire to do anything"), and physical activity (three items, e.g., "I don't do much during the day"). The items are scored on 7-point Likert scales (with 1 indicating best function and 7 worst function). In the literature a score above 37 – 40 points on the subscale subjective fatigue is quantified as "fatigued" [36].

Daily activity diary

Patients were instructed to keep a 3-day activity record (two week days and one Saturday) [7]. For each 15-min period, patients had to qualify their physical activity on a scale from 1 to 9 (1 = sleeping, 2 = sitting, 3 = standing, 4 = walking indoors, 5 = walking outdoors, 6 = leisure activities with low intensity, 7 = leisure activities with mild intensity, 8 = leisure activities with high intensity, 9 = sports activities with a high to maximal intensity). The physical activity level was calculated as the ratio between the sum of the physical activity scores and the resting activity scores (physical activity/rest).

Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 12.0, SPSS Inc, Chicago, IL, USA). Z-scores were calculated using the difference between the score of each individual patient and the reference values for age and gender, divided by the standard deviation of the reference values. Z-scores were tested using one-sample *t*-tests. Between-group comparisons (between gender and between gender and between plateau and non-plateau patients) were made using independent samples *t*-tests.
Associations between variables were calculated using linear regression (backward elimination method) or Pearson correlation coefficients. Alpha level was set at $p < .05$ for all analyses.

Results

Borderline significant differences in anthropometrical characteristics were found between children and adolescents with CFS and controls (**Table 1**). Patients had a borderline higher weight for age and BMI for age ($0.1 > p > 0.05$).
All exercise tests were performed without complications. No desaturation was observed during exercise. Only one of 20 (5%) patients had a large decrease in absolute $\dot{V}O_{2peak}$ (Z-score < – 2 SD), whereas 6 of 20 (30%) patients had a large decrease in $\dot{V}O_{2peak/kg}$ and 4 of 20 (20%) of the patients had a reduced W_{peak}. The Z-scores for HR_{peak}, RER_{peak}, $\dot{V}O_{2peak}$, $\dot{V}O_{2peak/kg}$ and W_{peak} can be appreciated from **Table 2**, and show a small reduction in

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Table 1 Comparison of anthropometrical measurements to reference values

	CFS patients mean ± SD (range)	Z-score mean ± SD	Ref values mean ± SD (range)	p value
Height (cm)	164.4 ± 20.0 (122.5 – 204.5)	0.19 ± 1.56	163.7 ± 15.2 (123.9 – 184.1)	0.60
Weight (kg)	56.5 ± 20.2 (22.9 – 97.8)	0.61 ± 1.38	51.7 ± 13.1 (23.3 – 64.2)	0.06
BMI ($kg \cdot m^{-2}$)	20.1 ± 3.8 (13.4 – 28.3)	0.59 ± 1.40	19.0 ± 2.0 (15.1 – 21.2)	0.08
Σ7 skinfolds (mm)	106.8 ± 46.0 (39.0 – 200.5)	0.49 ± 1.4	90.7 ± 35 (44.2 – 175.0)	0.14

Table 2 Comparison of exercise capacity and blood pressure data to reference values

	CFS patients mean ± SD (range)	Z-score mean ± SD	Ref values mean ± SD	p value
Exercise capacity				
RER_{peak}	1.21 ± 0.11 (1.00 – 1.35)	– 0.07 ± 1.36	1.21 ± 0.3	0.82
HR_{peak} ($b \cdot min^{-1}$)	182.9 ± 12.3 (160 – 209)	– 1.48 ± 1.66	194.9 ± 3.56	0.001
W_{peak} (Watt)	191.4 ± 64.9 (91 – 339)	– 0.93 ± 1.29	216.3 ± 59.5	0.07
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	2.07 ± 0.81 (0.90 – 4.21)	– 0.33 ± 1.0	2.19 ± 0.59	0.17
$\dot{V}O_{2peak/kg}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	37.7 ± 9.77 (22.5 – 55.8)	– 1.13 ± 1.41	43.59 ± 5.2	0.002
Blood pressure				
SBP rest (mmHg)	113.5 ± 13.5 (96 – 135)	– 0.91 ± 1.13	123.5 ± 8.9	0.002
DBP rest (mmHg)	67.9 ± 2.131 (54 – 94)	– 0.59 ± 1.20	69.9 ± 2.13	0.50
SBP at peak (mmHg)	142.5 ± 18.5 (111 – 167)	– 1.09 ± 1.43	156.3 ± 14.7	0.004
DBP at peak (mmHg)	73.7 ± 12.8 (51 – 103)	– 0.88 ± 1.58	80.5 ± 4.23	0.026

Abbreviations: W_{peak}: peak work load, HR_{peak}: peak heart rate, $\dot{V}O_{2peak}$ = peak oxygen uptake, $\dot{V}O_{2peak/kg}$: peak oxygen uptake per kilogram bodymass, SBP = systolic blood pressure, DBP = diastolic blood pressure

$\dot{V}O_{2peak}$ and W_{peak} and a moderate reduction in HR_{peak} and $\dot{V}O_{2peak/kg}$ in patients with CFS.

The differences in $\dot{V}O_{2peak}$, tended to differ significantly between males and females, with boys performing better than girls (mean difference Z-score $\dot{V}O_{2peak}$ 0.83, $p = .08$). There was no significant difference in W_{peak} and $\dot{V}O_{2peak/kg}$ values between boys and girls ($p = 0.9$ and $p = 0.14$ respectively)

A $\dot{V}O_2$ plateau was observed in 11 of the 20 patients. There were no significant differences in HR_{peak}, RER_{peak} and blood pressure between patients with and without a $\dot{V}O_2$ plateau (▶ **Table 3**). Blood pressures before and after exercise were significantly reduced compared to controls, except for diastolic blood pressure at rest (▶ **Table 2**). Peak blood pressure was not related with HR_{peak}, $\dot{V}O_{2peak}$ or $\dot{V}O_{2peak/kg}$. In a telephone follow-up, none of the patients reported excessive fatigue levels in the three days after the exercise test.

As displayed in ▶ **Table 2**, there was a no significant difference between the patients with and without a $\dot{V}O_2$ plateau in W_{peak} and $\dot{V}O_{2peak}$, ($p = 0.18$ and $p = 0.23$ respectively). However, patients with a $\dot{V}O_2$ plateau scored borderline significantly higher $\dot{V}O_{2peak/kg}$ compared to the patients without a $\dot{V}O_2$ plateau ($p = 0.05$), but had no statistically different fatigue levels ($p = 0.12$). Moreover, there was no significant difference in weight or BMI between the two groups. The resting blood pressures and blood pressures at peak exercise were not different between the patient with and without a plateau ($p > 0.7$)

The mean oxygen pulse ($\dot{V}O_{2peak}/HR_{peak}$) was 11.2 ± 4.1 (range 5.6 – 21.9) $mL \cdot beat^{-1}$, and represented 100 ± 22.3 (range 57 to + 163) percent of the predicted value. The mean score of the subjective fatigue questionnaire (CIS-20) was 45.7 ± 18.0 (range 25 – 107) points, indicating that all patients had an increased fatigue score on this questionnaire compared to a normative sample of school children [34]. The only significant predictors of total CIS-20 score were Z-score for systolic blood pressure at peak exercise and age. Both variables were positively related with CIS-20 score, however, the explained variance was only 43 %.

Table 3 Differences in exercise responses between the patients with and without a $\dot{V}O_2$ plateau

	$\dot{V}O_2$ plateau	Mean	SD	p value
RER_{peak}	no	1.23	0.11	
	yes	1.19	0.11	0.35
HR_{peak}	no	– 1.49	2.27	
($beats \cdot min^{-1}$)Z-score	yes	– 1.48	1.07	0.99
$\dot{V}O_{2peak}$	no	– 0.64	0.91	
($L \cdot min^{-1}$) Z-score	yes	– 0.08	1.10	0.23
$\dot{V}O_{2peak/kg}$	no	– 1.78	1.09	
($mL \cdot min^{-1} \cdot kg^{-1}$) Z-score	yes	– 0.60	1.47	0.05
W_{peak}	no	– 1.34	1.18	
(Watt) Z-score	yes	– 0.52	1.33	0.18
Fatigue (Cis-20)	no	53	22.2	
	yes	40	12.6	0.12

Daily activity diary showed that the patients were very inactive, spending most of the day lying or sitting, playing computer games or watching television. As can be appreciated from ▶ **Fig. 1**, there was a moderate association between exercise capacity and physical activity. The correlations between $\dot{V}O_{2peak}$, $\dot{V}O_{2peak/kg}$ and physical activity scores were $r = 0.47$ and $r = 0.60$ ($p < 0.05$) respectively. There was no significant difference in physical activity levels between the patients with and without a $\dot{V}O_2$ plateau ($p = 0.7$).

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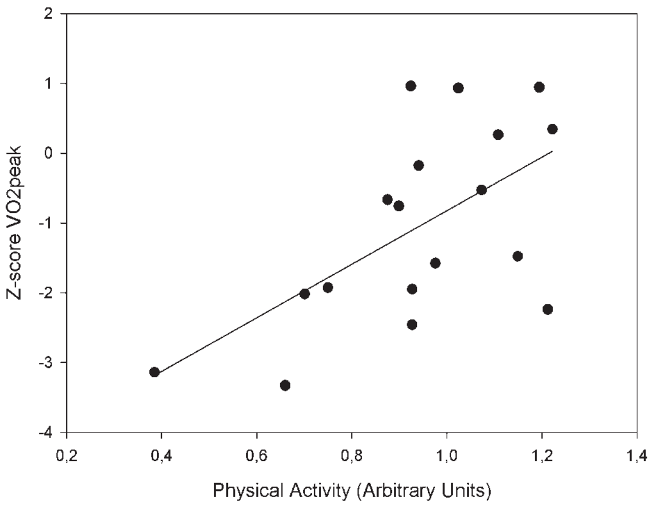

Fig. 1 The relationship between physical activity and $\dot{V}O_{2peak/kg}$ (r = 0.6; p < 0.008). Note: Physical activity data of two patients were missing.

Discussion

To our knowledge this is the first study examining the exercise capacity in children and adolescents with CFS. $\dot{V}O_{2peak}$ and W_{peak} were only marginally reduced in children and adolescents with CFS, and only a low percentage (5–30%) of the patients had an exercise capacity lower than −2 SD compared to normal. $\dot{V}O_{2peak/kg}$ was somewhat more reduced compared to $\dot{V}O_{2peak}$, which might be related to the increased BMI in some of the patients [22]. Three patients were obese as measured by the BMI Z-score for gender and age. The significant association between exercise capacity and physical activity, suggests a link between physical inactivity and fitness (deconditioning). It is well known from the literature that physical inactivity leads to a deterioration of exercise capacity [28,29,38]. Moreover, a case report of an ultra endurance cyclist who developed CFS suggest that the performance decrements of this athlete during his disease were the result of detraining, rather than an impairment of aerobic metabolism due to CFS per se [26]. Historically, a $\dot{V}O_2$ plateau has been regarded as the primary criterion for maximal oxygen uptake [33]. Fifty-five percent of our patients reached a $\dot{V}O_2$ plateau. This percentage is comparable with other studies in healthy children and adolescents [2]. The patients who showed a $\dot{V}O_2$ plateau did not have a higher $\dot{V}O_{2peak}$ or $W_{max/kg}$ but did not have lower fatigue levels compared to the patients without a $\dot{V}O_2$ plateau. However, $\dot{V}O_{2peak/kg}$ was significantly lower in patients who did not show a $\dot{V}O_2$ plateau. It has been suggested that a $\dot{V}O_2$ plateau is dependent on high pain and fatigue tolerance of patients [39]. However, the perceived fatigue levels (CIS-20) of the patients who demonstrated a plateau were not significantly different from the patients without a $\dot{V}O_2$ plateau. Moreover, the two groups were not different with regard to HR_{peak} and RER_{peak}, making the two groups undistinguishable based on these secondary $\dot{V}O_{2max}$ criteria [16]. Further studies should include a larger sample size, since some of the differences did not reach statistical significance, which might be related to the low patient numbers in the subgroup analysis.

We observed a reduced HR_{peak} during exercise testing, which paralleled previous observations during exercise testing in adult CFS patients [25]. Additionally, a reduced blood pressure before and after exercise was measured. Since blood pressure is dependent on heart rate and peripheral resistance, these results might indicate that the hemodynamics of children and adolescents with CFS might be altered. Both phenomena might be a result of an autonomic dysregulation providing a physiological basis for the disease symptoms. In a previous study in Gulf War veterans with chronic fatigue, a defect in cortical control of cardiovascular function (blood pressure and peripheral resistance) during stress tests was suggested to be a physiological basis for fatigue symptoms [23]. The significant association between the measured levels of fatigue and the blood pressure at peak exercise in the current study shows the importance of hypotension in the disease symptoms. Other studies have reported an association between neurally mediated hypotension and fatigue as well [20,27].

An often reported clinical symptom in CFS patients is a slow recovery from repeated bouts of exercise. In a telephone follow-up none of our patients reported excessive fatigue levels in the three days after the exercise test. This is in concordance with previous studies measuring physical activity levels in patients with CFS. These studies equally did not find exacerbation of fatigue after periods of increased physical activity [32]. Repeated exercise testing on one day, as has been performed in overtrained athletes [21] might shed further light on the reduced recovery rate and fatigue symptoms after exercise in patients with CFS.

The wide range of Z-scores in exercise and hemodynamic data make generalizability of the current results to the general childhood CFS population difficult. Some of the patients even scored above the mean values of the exercise tolerance reference values. However, the association between physical activity and exercise capacity, and hemodynamic data (blood pressure at peak exercise) and fatigue levels indicate that exercise testing could be used to monitor disease severity and symptoms.

In this study our patients were compared with reference values, as has been recommended in a recent position statement of the American Thoracic Society/American College of Chest Physicians [3]. Another approach would be the use of matched control subjects. However, a selection bias in control subjects could lead to results which might not be representative for the general population, especially when patients are matched with a sedentary group with comparable physical activity level [19]. The reference values in this current study are the best available reference values for healthy Dutch children and adolescents [6], and are comparable with other studies [9,41].

In conclusion, maximum exercise testing was feasible in young people with CFS. Maximal exercise capacity was only reduced in a minority of the patients and was related to current physical activity levels. Fatigue intensity of the patients was only associated with blood pressure at peak exercise and age. Future interventions in young people with CFS should focus on normalization of effort perception and reduction of autonomic dysregulation rather than improvement of exercise capacity.

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