Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity

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ABSTRACT

Background. Chronic fatigue syndrome (CFS) patients often complain that physical exertion produces an increase of complaints, leading to a greater need for rest and more time spent in bed. It has been suggested that this is due to a bad physical fitness and that physical deconditioning is a perpetuating factor in CFS. Until now, studies on physical deconditioning in CFS have shown inconsistent results.

Methods. Twenty CFS patients and 20 matched neighbourhood controls performed a maximal exercise test with incremental load. Heart rate, blood pressure, respiratory tidal volume, $O_2$ saturation, $O_2$ consumption, $CO_2$ production, and blood-gas values of arterialized capillary blood were measured. Physical fitness was quantified as the difference between the actual and predicted ratios of maximal workload versus increase of heart rate. Fatigue, impairment and physical activity were assessed to study its relationship with physical fitness.

Results. There were no statistically significant differences in physical fitness between CFS patients and their controls. Nine CFS patients had a better fitness than their control. A negative relationship between physical fitness and fatigue was found in both groups. For CFS patients a negative correlation between fitness and impairment and a positive correlation between fitness and physical activity was found as well. Finally, it was found that more CFS patients than controls did not achieve a physiological limitation at maximal exercise.

Conclusions. Physical deconditioning does not seem a perpetuating factor in CFS.

INTRODUCTION

Chronic fatigue syndrome (CFS) is defined as a severe fatigue lasting for at least 6 months, for which no somatic explanation can be offered and which leads to severe disability in daily life. CFS patients often complain that physical exertion produces an increase in complaints, leading to a greater need for rest and more time spent in bed. In some CFS studies it has been argued that muscle deficits might cause this fatigue after activity (Schwartz et al. 1978; Arnold et al. 1984; Jamal & Hansen, 1985). More recent studies on physical exercise in CFS showed that the neuromuscular mechanism is intact (Lloyd et al. 1988, 1991; Rutherford & White, 1991; Gibson et al. 1993; Kent-Braun et al. 1993; Lane et al. 1998).

Wessely et al. (1989) hypothesized that physical deconditioning might play an important role in CFS. The rationale was that because CFS patients experience a worsening of complaints after activity, they learn to avoid activity in order to prevent an increase of complaints. Being inactive, however, results in a decrease of physical fitness. This means that over time...
complaints get worse at an increasingly lower level of physical activity. In this way a vicious and perpetuating circle might be established, resulting in a decreasing physical fitness. Based on this hypothesis, the role of (avoidance of) physical activity in CFS has been emphasized more and more (Wagenmakers, 1999). In cognitive behavioural therapy (Sharpe et al. 1996; Deale et al. 1997) as well as in graded exercise therapy (Fulcher & White, 1997) a gradually increasing activity programme is of main importance. One might wonder, however, whether improving physical fitness is an essential factor in CFS, or whether other factors determine treatment effects. If physical fitness is an important and perpetuating factor in CFS, one would not only expect CFS patients to have a worse physical fitness, but one would also expect a negative relationship between physical fitness and fatigue and impairment and a positive relationship between physical fitness and physical activity. Studies on aerobic or cardiocirculatory deconditioning in CFS have shown contradictory results (Montague et al. 1989; Riley et al. 1990; Cordero et al. 1996; Sisto et al. 1996; Freeman & Komaroff, 1997; De Lorenzo et al. 1998). These differences might be due to differences in tests, sample sizes and patient and control selection. Differences in tests used make it difficult to compare results. However, the most important reason for the inconsistencies found seems to be the use of an inappropriate control group in most studies. Physical fitness in CFS should not be compared with selected healthy and rather active controls. To deal with this problem, Sisto et al. (1996) used sedentary controls. In our study, well-matched neighbourhood controls are used. Although inconsistencies exist in the findings concerning physical fitness, most studies are consistent in their findings, that at least part of the CFS patient sample does not attain a physiological limitation on a maximal exercise test. The aims of the present study are to determine whether CFS patients have a worse physical fitness as compared to matched neighbourhood controls, and whether there is a negative relationship between physical fitness and fatigue and impairment and a positive relationship between physical fitness and physical activity. We also investigated whether CFS patients attain a physiological maximum on a maximal exercise test.

METHOD

Subjects
Patients diagnosed at the General Internal Medicine outpatient clinic of the University Hospital Nijmegen, who already agreed to participate in scientific studies, were asked to participate. Patients were diagnosed as having CFS if they fulfilled the Fukuda criteria (Fukuda et al. 1994). In addition, CFS patients were only included if they had a CIS fatigue severity score of ≥ 40 and a total score on the eight SIP subscales used of ≥ 800, to guarantee severe fatigue and disability (see instruments; Vercoulen et al. 1994). Patients invited for the current study were further selected on whether they lived in the surroundings of our hospital, because a heart rate monitor was brought to the patients’ and controls’ home a day before the exercise test and was picked up again 1 day after the test. None of the patients refused. All patients were asked to invite a neighbour of the same gender and about the same age as a control person. Twenty of 26 CFS patients fulfilled our additional criteria of the CIS and the SIP and found a neighbourhood control of about the same age and the same sex. So 20 CFS patients and 20 matched neighbourhood controls participated.

Instruments

Fatigue
Fatigue was measured by the subscale fatigue severity of the fatigue questionnaire Checklist Individual Strength (CIS) (Vercoulen et al. 1994). This scale consists of 8 items concerning fatigue during the last 2 weeks. Each item is scored on a 7-point Likert scale, so the range is 8–56.

Functional impairment
The Sickness Impact Profile (SIP) (Bergner et al. 1981; Jacobs et al. 1990) was used to assess functional impairment. This questionnaire measures the influence of complaints in different areas of daily functioning. Eight subscales were used (alertness behaviour, sleep, homemaking, leisure activities, work, mobility, social interactions and ambulation).

Physical activity
This was measured using the actometer
(Vercoulen et al. 1997). The actometer is an apparatus worn around the ankle for 2 weeks, recording the amount of movements every 5 min. The actometer consists of a piezoelectric sensor. Acceleration of the sensor results in an output signal. This information is stored to an internal memory, and can be read by use of a personal computer. The mean actometer score for the days that the actometer was worn before the exercise test was used to assess the level of physical activity.

**Exercise test**
A bicycle ergometer test with incremental load was used as an exercise test. The workload was increased every minute in steps of 10% of estimated maximal workload, in order to complete the maximal exercise test in approximately 10 min (Folgering et al. 1988). The steps varied from 10 to 30 watt/min. Subjects were instructed to go on until they could no longer continue. They were verbally encouraged to perform maximally. During this test, heart rate, blood pressure, respiratory tidal volume, O₂ saturation, O₂ consumption, CO₂ production, and blood-gas values of arterialized capillary blood (before and after exercise, at minute 3, 6, and 9 of the exercise and at maximal workload) were measured. Every 3 min and at maximal workload, the modified Borgscale was used to assess the rate of perceived exertion (Borg et al. 1985). On a scale from 1 to 10, patients were asked to indicate how difficult it was to perform the pedalling exercise. The intensity of anaerobic workload was measured from the difference in base excess at rest and 3 min after maximal workload, which represents the produced lactate within the cells of the leg muscles. Achieved maximal workload (W) was compared with the predicted value. The predicted maximal workload was calculated from:

\[ W_{\text{max pred}} = \frac{V_{O_2,\text{max pred}} - V_{O_2,\text{rest pred}}}{10.29} \]

(Wasserman et al. 1994).

In this formula, predicted maximal ventilatory O₂ uptake (\(V_{O_2,\text{max pred}}\)) is related to height (\(H\)/cm), age (A/year) and sex (S/m = 0, f = 1):

\[ V_{O_2,\text{max pred}} (l/min) = 0.046H - 0.021A - 0.62S - 4.31 \]

(Jones et al. 1985), and

\[ V_{O_2,\text{rest pred}} = 0.25 l/min \]

(Astrand et al. 1986).

Maximal heart rate (HR) was compared with the predicted maximal heart rate, depending on age (A/year):

\[ HR_{\text{max pred}} (\text{beats/min}) = 220 - A \]

(Wasserman et al. 1991).

Fitness was defined as the differences in slope of the relationships between heart rate and external workload of the individual subject versus a normalized slope. Fit subjects have relatively low heart rates at a certain workload and vice versa (McArdle et al. 1991). In formula:

\[ \frac{W_{\text{max}}}{HR_{\text{max}} - HR_{\text{rest}}} = \frac{W_{\text{max pred}}}{HR_{\text{max pred}} - HR_{\text{rest}}} \]

A negative outcome indicates a fitness that is worse than would be expected; a positive outcome indicates a better fitness than expected.

Subjects were considered attaining a physiological limitation if one of the following criteria was met: (1) attainment of predicted maximal heart rate; (2) increase of base excess at 3 min after maximal workload compared with base excess at rest (lactate production) of more than 10 mmol/min; (3) increase of CO₂ pressure in blood at maximal workload compared with the value at rest.

**The 24 hours heart rate**
This was assessed using a Polar sport tester. The Polar sport tester consists of a belt around the chest, containing ECG electrodes, amplifier and transmitter, and a watch. The ECG signals are sent to the watch, recording the R-tops in an internal memory every 60 s, during 24 h. For the analysis in this study mean scores of every half an hour were used. The Polar sport tester was brought to the patients’ and controls’ home to wear during the 12 hours preceding the start of the ergometer test. After the ergometer test the Polar sport tester was worn for another 12 hours. Then the sport tester was collected from the subjects’ homes.

For six controls and four CFS patients almost all data of the Polar sport testers were missing, probably because of pressing the buttons accidentally during sleep. Also, 10 subjects (one
CFS patient and nine controls) had incidental missing data. In these cases (1.7% of all sport tester data) missing values were replaced by the mean value of the half hour scores before and after the missing value of the particular subject.

Statistical analysis
Differences between groups were tested using one-way analysis of variance (ANOVA) or repeated measures ANOVA for ratio variables. The Mann-Whitney U test was used in case of skewed variables, \( \chi^2 \) was used for dichotomous variables. Fisher’s Exact Test was used when > 20% of the cells had an expected count < 5. Before Pearson correlation coefficients were computed, skewed variables were transformed. To test whether the correlations obtained for CFS and for controls were significantly different, both correlations were converted to Fisher’s \( z \) and the difference between them was divided by the standard error of the difference to yield a normal curve deviate (Howell, 1997). For all tests, the significance level was set at \( P < 0.05 \).

RESULTS
Patient and control characteristics
Demographic data, height, weight, fatigue severity, functional impairment and physical activity are displayed in Table 1. There were no significant differences in gender, age, height and weight. On fatigue severity, functional impairment and physical activity differences were found as expected. Mean duration of complaints in CFS was 3.2 years (±2.5).

Fitness
CFS patients had a mean fitness of \(-0.32 ± 0.50\) watts/beat and their controls had a mean fitness of \(-0.22 ± 0.82\) watts/beat (non-significant: Mann–Whitney U test, \( P = 0.25 \)). Nine of the 20 CFS patients had a better fitness than their own control. In Fig. 1 a boxplot of fitness in CFS and controls is displayed.

Oxygen consumption and CO\(_2\) production
Table 2 shows the O\(_2\) and CO\(_2\) uptake and production. CO\(_2\) pressure in the blood declined more for CFS than for controls (\( P = 0.03 \)). There were no other significant interaction effects for the respiratory exchange variables.

Heart rate
Heart rates from 12 h before the test up to 12 h after the test for CFS and their controls are displayed in Fig. 2. No significant interaction effect was found.

Table 1. Characteristics (% or mean (s.d.)) of CFS patients (N = 20) and controls (N = 20)

<table>
<thead>
<tr>
<th></th>
<th>CFS</th>
<th>Controls</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, %</td>
<td>60</td>
<td>60</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.1 (8.3)</td>
<td>32.8 (7.2)</td>
<td>0.59</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.7 (9.4)</td>
<td>174.8 (9.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.0 (16.4)</td>
<td>71.5 (14.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Fatigue (CIS; range 8–56)</td>
<td>51.7 (5.1)</td>
<td>13.4 (5.1)</td>
<td>0.00*</td>
</tr>
<tr>
<td>Functional impairment (SIP-8)</td>
<td>1743 (1249–2058)</td>
<td>0 (0–0)</td>
<td>0.00*</td>
</tr>
<tr>
<td>Physical activity (actometer)†</td>
<td>58.2 (27.2)</td>
<td>99.5 (25.0)</td>
<td>0.00*</td>
</tr>
</tbody>
</table>

\( \chi^2 \) for % female; Mann–Whitney U test for SIP, medians (25th and 75th percentile) presented, one-way ANOVA for other variables.
† Deviating \( N \) because of falling actometers. \( N = 15 \) for CFS and \( N = 18 \) for controls.

* \( P < 0.05 \).
Fitness and relations with fatigue, impairment and physical activity

For CFS as well as for controls a significant correlation of −0.45 was found between fitness and fatigue (P = 0.049 and 0.044 respectively). In CFS significant correlations between fitness and functional impairment (r = −0.49, P = 0.027) and fitness and physical activity (r = 0.54, P = 0.039; N = 15 because of failing actometers) were found as well. Because 85% of the controls had a functional impairment score of zero, a correlation between functional impairment and fitness could not be computed. The correlation between fitness and physical activity in controls was non-significant (r = 0.28, P = 0.260; N = 18 because of failing actometers). The difference in the correlations between fitness and physical activity in CFS and in controls (0.54 and 0.28 respectively) were statistically non-significant (P = 0.414).

Exercise capacity

Neither the duration of the maximal bicycle ergometer test nor achieved workloads were significantly different for CFS and controls (Table 3). However, there was a statistically significant difference for the percentage of the predicted workload reached, being lower in
CFS. On average, CFS patients reached 70% of their predicted workload, whereas the controls reached 83% of their predicted value. For heart rate scores during exercise, no statistically significant differences were found.

**Attaining a physiological limitation**

Of the CFS patients 55% performed up to a physiological limitation, compared with 80% of the controls (this difference was not significant, Table 4).

**Perceived exertion**

Not all subjects performed the maximal exercise test for 6 min or more. Therefore, Borgscale scores were compared 3 min after starting the test and at maximal workload only. Scores on the Borgscale 3 min after starting the test were 3.82 ± 0.88 for CFS (N = 17) and 2.44 ± 0.86 for controls (N = 18). At maximal workload Borgscale scores were 8.76 ± 1.68 for CFS and 7.33 ± 2.11 for controls. There was a significant within subjects effect (P = 0.00; F = 210.06; df = 1). No significant interaction effect was found (P = 0.94; F = 0.01; df = 1).

**DISCUSSION**

In the present study CFS patients did not have a worse physical fitness compared with their controls. Both groups had a lower physical fitness than would be expected according to height, age and sex. This particularly emphasizes the importance of a well-matched control group. In our study, the fitness score of one of the controls was an extreme. When this extreme is excluded from the analysis, the difference remains statistically non-significant. One might suggest that not finding a significant difference in fitness is due to a power problem, because of sample sizes. However, almost half of the CFS patients had a better fitness than their own control. This result underlines the conclusion that there is no difference in fitness between CFS patients and their controls. Our finding agrees with that of Sisto *et al.* (1996), who found that CFS patients had a low but normal fitness, comparable to sedentary controls. Another objection might be that in spite of substantial and expected differences in fatigue, functional impairment and level of activity, only a selected group of patients was included. Bedridden patients, in particular, are unlikely to participate in these scientific studies. Van der Werf *et al.* (2000) recently found that passive patients can be distinguished from the relatively active patients based on the actometer. In the present study three passive CFS patients participated. These patients resemble bedridden patients.

Concerning respiratory variables it was found that the CO₂ pressure in the blood of CFS patients decreased more than in the controls. This might indicate that CFS patients tend to hyperventilate during exercise. In other studies it was found that hyperventilation, although prevalent in a substantial part of the cases, does not seem to play an essential role in CFS (Saisch *et al.* 1994; Bazelmans *et al.* 1997). However, no other significant differences were found concerning oxygen consumption and carbon dioxide production. In addition, according to Wasserman *et al.* (1994) oxygen consumption should be 10.29 (± 1) ml per min per watt for normal subjects. If we compute millilitre oxygen consumption per minute per watt for the subjects in our study (O₂ consumption at maximal workload minus O₂ consumption at rest multiplied by 1000 and divided by maximal workload reached) this is 9.94 (± 1.31) for CFS patients and 9.71 (± 1.41) for controls. These values are both very similar to the normal value of Wasserman *et al.* (1994). Very unfit subjects usually need more O₂ per watt. Consequently, this finding adds to the conclusion that the fitness of the CFS patients is not substantially impaired.

The maximal workload reached during an incremental bicycle ergometer test did not differ between CFS patients and controls, neither did...
Is physical deconditioning a perpetuating factor in CFS?


