Exercise Capacity in Chronic Fatigue Syndrome

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Background: Patients with chronic fatigue syndrome (CFS) suffer from various symptoms, including debilitating fatigue, muscle pain, and muscle weakness. Patients with CFS can experience marked functional impairment. In this study, we evaluated the exercise capacity in a large cohort of female patients with CFS.

Methods: Patients with CFS and matched sedentary control subjects performed a maximal test with graded increase on a bicycle ergometer. Gas exchange ratio was continuously measured. In a second stage, we examined only those persons who achieved a maximal effort as defined by 2 end points: a respiratory quotient of at least 1.0 and an age-predicted target heart rate of at least 85%. Data were assessed using univariate and multivariate statistical methods.

Results: The resting heart rate of the patient group was higher, but the maximal heart rate at exhaustion was lower, relative to the control subjects. The maximal workload and maximal oxygen uptake attained by the patients with CFS were almost half those achieved by the control subjects. Analyzing only those persons who performed a maximal exercise test, similar findings were observed.

Conclusions: When compared with healthy sedentary women, female patients with CFS show a significantly decreased exercise capacity. This could affect their physical abilities to a moderate or severe extent. Reaching the age-predicted target heart rate seemed to be a limiting factor of the patients with CFS in achieving maximal effort, which could be due to autonomic disturbances.

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A diagnosis of chronic fatigue syndrome (CFS), as defined in 1994 by the Centers for Disease Control and Prevention (CDC), Atlanta, Ga, requires unexplained fatigue for more than 6 months not due to continuing exertion, not resolved by rest, and accompanied by 4 or more of the following 8 symptoms: sore throat, tender lymph nodes, memory and concentration problems, joint pain, headache of a new type, unrefreshing sleep, and post-exertional malaise lasting more than 24 hours. Chronic fatigue syndrome is characterized as a new onset of fatigue, serious enough to reduce daily activities by more than 50% and in the absence of any other medically identifiable disorders. Patients with CFS exhibit marked impairment and sometimes have greater degrees of functional disability than do patients with other diseases such as type 2 diabetes mellitus, congestive heart failure, hypertension, acute myocardial infarction, major depression, relapsing or remitting multiple sclerosis, and acute infectious mononucleosis.

Various studies have evaluated the ability of patients with CFS to perform exercise, but conflicting results have been published. Some authors believe the aerobic capacity of patients with CFS lies within the low normal range, whereas others report a reduced aerobic capacity relative to normal subjects and to patients with irritable bowel syndrome. Taking into account that the population with CFS is very heterogeneous, these different findings could be due to a selection bias, the low number of individuals studied, or both.

The aerobic potential of an individual is determined by cardiac output and muscle oxidative capacity. Muscle contractility also plays a very important role. Previous studies have considered whether these factors limit the ability to complete physically active tasks in CFS. Although patients report significant reductions in physical capabilities and post-exertional symptom exacerbation,
findings from their tests of muscle strength, endurance, and function are normal.\textsuperscript{9,12,17-21} Histological and metabolic studies give mixed results. Several studies of patients with CFS have shown reductions in muscle oxidative capacity and metabolism,\textsuperscript{16,22} atrophy of the fast twitch fibers,\textsuperscript{23-25} mitochondrial abnormalities,\textsuperscript{23,24,26} increased lactic acid production during exercise,\textsuperscript{13-15} and myopathic features on single fiber electromyogram.\textsuperscript{27}

However, these abnormalities are not consistent, contributing to the consensus that CFS is a heterogeneous disorder and that differences in patient populations and muscles studied may account for discrepancies between studies.\textsuperscript{28} Some authors believe that central rather than peripheral factors are responsible for the reduced physical capacity and the difficulty in performing a maximal effort.\textsuperscript{9,11,17,29} Patients with CFS have exhibited repetitively negative changing T waves at Holter registrations\textsuperscript{30} and a slow acceleration of heart rate during exercise.\textsuperscript{10} It is suggested that the fatigue in CFS may be related to subtle cardiac dysfunction occurring at workloads common to ordinary living.\textsuperscript{30}

The pathophysiology of exercise has been studied extensively in relation to cardiovascular, pulmonary, endocrine, and neuromuscular diseases, but little information exists on the interrelationship between physical exercise parameters and CFS.\textsuperscript{31} As there is only scant information on the physical capacity of patients with CFS, physicians who are called on to assist in the determination of the physiological capacity of these patients have no standards to rely on. The few studies that have been done involve limited numbers of patients, which could bias the results considering the heterogeneity of the CFS

METHODS

PATIENTS AND CONTROL SUBJECTS

A total of 450 consecutive female patients who met the CDC's 1988 or 1994 criteria for CFS were enrolled in the study, which had been approved by an ethical committee. Of these, 427 met the requirements and agreed to participate. The diagnosis of CFS was made by patient history, routine physical examination, and laboratory test results to exclude other relevant diagnoses, as recommended by Fukuda et al.\textsuperscript{1}

A group of 204 age-matched sedentary women served as a control population. We selected them from subjects who came for medical checkups. Only those who did sitting work and performed a maximum of 1 hour of sports per week were included. Control subjects were accepted into the study only if they denied having symptoms of chronic fatigue and did not suffer from any medical conditions known to cause chronic fatigue.

STUDY DESIGN

All patients and controls underwent a bicycle ergometric test against a graded increase in workload until exhaustion. The exercise tests were performed at room temperature (20\textdegree C-22\textdegree C) and at a humidity of 40\% to 60\%. The subjects assumed the sitting position on the electromagnetically braked ergometer (Jaeger 900; Lode B.V., Groningen, the Netherlands), and the test was started after 3 to 5 minutes of adjustment. Heart rate was continuously monitored at rest and during exercise. There was continuous recording of the 12-lead electrocardiogram using an electrocardiograph (Marquette Electronics Inc, Milwaukee, Wis). An open circuit spirometer (Mijnhart Oxycon; IBM, Bunnik, the Netherlands) with automatic printout every 30 seconds was used to collect pulmonary data during the test. As such, data for \( V_{\text{O}_2}\text{max} \) and maximal carbon dioxide production were averaged for every 30-second interval during each stage. Expired air was collected via a 2-way breathing valve attached to a mask that covered the subject's nose and mouth and was analyzed continuously for ventilatory and metabolic variables. Before each test, the spirometer was calibrated for ambient conditions.

The increments were chosen to obtain a total exercise duration between 8 and 12 minutes, which is suggested as an optimal test period.\textsuperscript{34} Thus, the duration of exercise was kept below 15 minutes to avoid possible early onset fatigue in the lower limbs because of lack of physical fitness. The patients with CFS started at 10 W, with an increase of 10 W/min. The control population began at 40 W, with an increase of 30 W every 3 minutes.

The following parameters were measured: heart rate at rest (HRrest), maximal heart rate (HRmax), maximal work capacity attained, \( V_{\text{O}_2}\text{max} \) per kilogram of body weight, maximal respiratory quotient (RQmax), heart rate at RQ of 1.0 (HRAT), peak work rate at RQ of 1.0 (WAT), and the percentage of target heart rate (THR) that was achieved. The metabolic data analyzed were the means of the last 30 seconds from the final stage of exercise or the highest value attained if a decline in \( V_{\text{O}_2} \) occurred at the final workload.

A separate analysis between patients and controls was done with all those who performed a maximal exercise test. The criteria used for determining whether the subject had attained a physiological maximum were the accomplishment of 2 end points: (1) an RQ greater than 1.0 and (2) reaching at least 85\% of the age-predicted THR. The HRmax achievable during exercise of large muscles (eg, with use of a bicycle ergometer) is generally equivalent to 220 minus the subject's age in years, plus or minus 20 beats per minute.\textsuperscript{35}

Data were sent to Neil McGregor, MD, PhD, at the University of Newcastle, Australia, for independent analysis to reduce any possibility of bias.

STATISTICAL ANALYSIS

Data distributions were evaluated for violations of assumptions with parametric statistical analyses. The percentage of THR was arcsine transformed, while all other exercise response variables were log transformed to improve normality and linearity. Subject characteristics were assessed using \( \chi^2 \) probability and \( t \) tests. Univariate group differences were evaluated on untransformed data using the non-parametric Mann-Whitney test. Multivariate group differences were determined on transformed data using standard and forward stepwise discriminant function analyses. Pearson product moment correlation was used to investigate within-group differences in the associations between variables. These data were processed using statistical software (Access\textsuperscript{97} and Excel\textsuperscript{97}; Microsoft, Redmond, Wash, and Statistica, version 3.1; Statsoft, Tulsa, Okla).
population. Therefore, we judged it necessary to study a large group of patients to be able to draw conclusions on their exercise capacity and degree of impairment.

The standard for measuring exercise capacity has always been the maximal oxygen uptake (VO₂max) during high intensity whole body exercise. It is generally accepted that cardiopulmonary exercise testing is a good research tool for this purpose and is commonly used to determine an individual’s exercise potential.34

We designed a maximal bicycle ergometric test against a graded increase in workload, which aimed to collect data regarding exercise capacity in a large cohort of female patients with CFS. These results were compared with a population of sedentary control female subjects and with findings reported in the literature on other sedentary healthy populations.

**RESULTS**

There was no difference in age between the patients with CFS and the control subjects (mean ± SD years, 37.0 ± 9.0 and 35.9 ± 9.2, respectively). All individuals in the study were white Europeans. Those with CFS had a mean illness duration of 7.0 ± 6.4 years.

Discriminant function analysis was applied to determine the major characteristics that differentiated between the exercise response profiles of the CFS vs the control subjects. **Table 1** shows that the regression model revealed a large deviation in the response characteristics between them (Wilks λ=0.14, F=199.4; *P*<.001), with a high degree of homogeneity within the 2 groups. Most (97.8%) of the control subjects complied with the control model profile, and 99.7% of individuals with CFS complied with the CFS group profile. Univariate analysis showed that 10 of the 15 exercise profile measures were reduced in those with CFS compared with the control subjects and 1 parameter (HRrest) was increased.

Forward stepwise discriminant function analysis was used to assess the major parameters that determined the different response characteristic profiles in the CFS vs the control groups. A strong model was found (Wilks λ=0.136, F=301.3), with HRAT being the primary discriminating variable, followed by WAT and the maximal workload per kilogram of body weight (*P*<.001 for all).

Thus, the exercise response characteristics of the CFS and the control subjects were very dissimilar, principally in HRAT and WAT.

Pearson product moment correlation analysis was undertaken to assess any differences in the exercise parameters between the 2 groups to allow a better understanding of how exercise capacity varied. **Table 2** summarizes the correlation comparisons between WAT and HRAT with the heart rate parameters and RQ in the patients with CFS vs the control subjects. There was a significant disregulation of the relationships between WAT and HRAT with disregulation of the heart rate parameters. Therefore, variation in heart rate was strongly related to changes in exercise capacity in the patients with CFS.

**Figure 1** shows the comparative scatterplot of WAT and HRAT in the 2 groups. While there was a similar correlation between WAT and HRAT (CFS, *r*=0.50; control, *r*=0.56; *P*<.001 for both), there was a large reduction in both parameters in the patients with CFS (Table 1). **Figures 2, 3, and 4** illustrate the association between HRAT and WAT, VO₂max, and exercise duration in the patients with CFS and in control subjects. These figures demonstrate that the relationships between these 3 factors were quite different in the 2 groups.

The maximal respiratory quotient was positively correlated with exercise duration, HRmax, and the percentage of THR in both groups (all *r*>0.25; *P*<.001). In the patients with CFS, RQmax was positively associated with WAT (*r*=0.26; *P*<.001) and negatively associated with HRAT (*r*=-0.15; *P*<.01). In the control individuals, RQmax was positively correlated with HRrest (*r*=0.17; *P*<.02) and negatively correlated with WAT (*r*=-0.24; *P*<.002).

The percentage of THR was positively associated with exercise duration, HRrest and HRmax, maximum workload, VO₂max, HRAT and WAT, and RQmax in both groups (all *r*>0.25; *P*<.001). In the control subjects, the percentage of THR was negatively correlated with the THR.
In those with CFS, the percentage of THR had a statistically higher correlation coefficient for WAT (CFS=0.63, control=0.15; P<.001, for difference) and maximum workload (CFS=0.53, control=0.28; P<.002, for difference) and a statistically lower correlation coefficient for HR AT (CFS=0.31, control=0.52; P<.007, for difference). Thus, in patients with CFS, the reduction in the percentage of THR achieved was associated with a reduction in workload capacity.

Those with CFS had a higher HRrest and a lower HRmax relative to the control subjects (Table 1), and therefore the increase from resting to maximum heart rate was calculated for the sake of comparison. It was lower in the patients with CFS vs the control subjects (CFS=62.5±19.0 beats per minute, control=88.9±14.4 beats per minute; P<.001). In the CFS group, the increase in heart rate from rest to maximum had a higher positive correlation with the maximum workload (CFS=0.68; control=0.45) and exercise duration (CFS=0.68; control=0.47) (P<.001 for all) compared with the control subjects.

In the second stage of the study, we examined only those persons who attained a maximal effort as defined by 2 end points: achievement of an RQ of at least 1.0 and an age-predicted THR of at least 85%. A relatively small percentage of patients with CFS, 37%, reached both criteria (Table 3). The target heart rate seemed to be the limiting factor, since only 41% of the patients achieved an HRmax of at least 85% of the age-predicted THR, whereas 80% of them reached the anaerobic threshold defined by a minimal RQ of 1.0. Thus, for comparison, we analyzed the metabolic data of those subjects who had achieved a maximal effort in both study groups (Table 4).

There was no difference in age between the 141 patients with CFS and the 158 control subjects (mean±SD years, CFS=36.2±9.4; control=35.5±9.0) who achieved maximal effort. Those with CFS had a mean illness duration of 6.8±7.0 years.

Discriminant function analysis was applied to determine the major differences between the exercise response characteristics of the patients with CFS vs the control subjects who achieved maximal effort. Table 4 shows that the regression model revealed a large difference in these characteristics (Wilks λ=0.10, F=158.8; P<.001), with a high degree of homogeneity within the 2 groups. All of

### Table 2. Pearson Product Moment Correlation Differences With the Primary Discriminant Parameters and Heart Rate Parameters and Respiratory Quotient in the CFS and Control Female Subjects*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Workload at Anaerobic Threshold</th>
<th>Heart Rate at Anaerobic Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CFS</td>
<td>Control</td>
</tr>
<tr>
<td>Maximum heart rate</td>
<td>0.37 (.&lt;001)</td>
<td>0.70 (.&lt;001)</td>
</tr>
<tr>
<td>% Target heart rate</td>
<td>0.33 (&lt;.001)</td>
<td>0.51 (&lt;.003)</td>
</tr>
<tr>
<td>Target heart rate</td>
<td>0.12 (.04)</td>
<td>0.14 (.05)</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>-0.07 (.63)</td>
<td>0.38 (&lt;.001)</td>
</tr>
<tr>
<td>Maximum respiratory quotient</td>
<td>-0.17 (&lt;.003)</td>
<td>-0.11 (.14)</td>
</tr>
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* CFS indicates chronic fatigue syndrome. Data are given as difference (P).
the control subjects complied with the control model profile, and 99.3% of the patients with CFS complied with the CFS group profile. Univariate analysis demonstrated that 8 of the 15 exercise profile measures were reduced in the CFS group relative to the control group and 2 were increased (HR_{rest} and WAT). Compared with the initial analysis in the entire study group, the patients with CFS who achieved maximal responses showed no difference in exercise duration. Most of the exercise parameters found to be dissimilar between the CFS and control groups were the same in patients who achieved maximal responses relative to those in the entire cohort of patients with CFS. Therefore, the exercise capacity in the patients with CFS who reached their maximal response was still quite different from that of the control subjects.

Forward stepwise discriminant function analysis was applied to evaluate the major parameters that determined the differences between the exercise response characteristic profiles of the CFS vs the control groups who achieved maximal effort. A strong model was found (Wilks \( \lambda = 0.11 \), \( F = 184.3 \)), with HR_{AT} being the primary discriminating variable, followed by WAT and maximal work-
Exercise capacity was evaluated in a large cohort of female patients with CFS and compared with that of sedentary control subjects. The VO_{2max} levels of our control group were consistent with various studies in untrained women of approximately the same age describing VO_{2max} levels of 30 to 36 mL/kg per minute. Our patients with CFS had an average VO_{2max} just below 20 mL/kg per minute, representing significant impairment relative to the controls. Comparing the exercise capacity in our patients with data from other studies shows a functionality similar to that of elderly healthy controls (60-69 years), individuals with chronic heart failure, patients with chronic obstructive or restrictive pulmonary disease, and those with skeletal muscle disorder. The decrease in physical capacity in patients with CFS appears to be associated with disease severity and is consistent with the reduction seen in many other chronic illnesses.

A major criterion for defining CFS is that patients report a greater than 50% reduction in activity levels relative to their pre-illness state. Maximal workload at exhaustion averaged 53% of normal in our patients with CFS, which is close to the 50% decrease in physical capabilities described in the CDC's criteria for CFS. Sisto and Riley and their colleagues reported only slight reductions in aerobic power on a graded treadmill test in female patients with CFS. Their patients had an average VO_{2max} of 30.1 mL/kg per minute and 31.7 mL/kg per minute, respectively, which places them within the range of sedentary control subjects according to the classification by MacAuley et al. We believe that the failure to assess the more severely affected patients appears to have led to a disparity in study conclusions about the exercise capacity in patients with CFS.

In contrast to many investigators who have claimed heterogeneity of laboratory and exercise findings when comparing their results with other CFS studies, our study shows a high degree of homogeneity within the CFS group in multivariate analysis. Our statistical homogeneity is an assessment of the differences between the 2 groups evaluated and does not necessarily reflect clinical homogeneity. The contradictions between our study and the heterogeneous findings in other studies may also result from the array of measures used, different study designs and numbers, and various interpretations given to the results of those investigations.

Only a small number of patients with CFS reached both parameters for maximal exercise testing (RQ >1.0 and HRmax >85% THR). However, when we analyzed the entire cohort data using only those subjects who fulfilled the criteria for maximal exercise, we still observed the same differences in exercise capacity between the CFS group and the control subjects. Multiple regression analysis showed that the same parameters differentiated between the CFS and control groups as in the cohort.

**Figure 4.** Categorized scatterplot of the differences in exercise duration and heart rate at the anaerobic threshold in chronic fatigue syndrome (CFS) and in control female subjects. The diagonal solid line represents 95% confidence interval (regression analysis); diagonal dashed lines, 95% confidence limits (1 SD).

**Table 3. Prevalence of CFS and Control Female Subjects Who Attained the Maximal Exercise Parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>CFS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>427 (100)</td>
<td>204 (100)</td>
</tr>
<tr>
<td>THR &gt;85%</td>
<td>174 (41)</td>
<td>174 (85)</td>
</tr>
<tr>
<td>RQ &gt;1.0</td>
<td>342 (80)</td>
<td>192 (94)</td>
</tr>
<tr>
<td>THR &gt;85% and RQ &gt;1.0</td>
<td>157 (37)</td>
<td>163 (80)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage). CFS indicates chronic fatigue syndrome; THR, target heart rate; and RQ, respiratory quotient.
The resting heart rate was higher in patients with CFS, as in other studies. Moreover, most of our patients were not able to achieve their age-predicted THR, a finding that is in agreement with some previous studies in CFS. Although some authors believe that the inability to reach the THR indicates incapability to exercise to full capacity, because of elevated perceptions of exertion or fatigue or physical deconditioning, a large percentage of our patients who did not reach their age-predicted THR did reach their RQ of 1.0. Furthermore, Gibson et al observed similar heart rates at increasing workloads in CFS and control subjects, which is more consistent with submaximal exertion than with deconditioning. The increase in HRest associated with a lower achieved HRmax suggests that alteration in cardiac function is a primary factor associated with the reduction in exercise capacity in CFS.

It is a peculiar finding that, although most of our patients reached the respiratory anaerobic threshold, fewer of them also reached their THR. This would also indicate that suboptimal cardiac function is a major limiting factor in exercise capacity in patients with CFS. Fischler et al use only the THR criteria to assess whether a patient did or did not perform a maximal effort. This would suggest that too great an emphasis is placed on the THR, especially since several studies suggest autonomic nervous system involvement in CFS that could influence the chronotropic cardiac systems. It could be that the increased HRest and the low HRmax are the result of a disturbed autonomic system. Possible disturbances include sympathetic predominance, diminished vagal power, and reduced sympathetic responsiveness to stress and exercise. Considering that 66% to 90% of patients with CFS initially develop an acute infectious illness, exercise bradycardia might also be related to post-acute viral status, either as a direct or indirect latent effect, and the possibility that cellular metabolic pathways are disrupted by the viral presence or by some immunological process triggered by the acute or persistent infection.

The exact mechanisms for this are speculative. It may be that loss of muscle protein contributes to the perceived muscle weakness. Cytokine abnormalities and dysfunction of the 2-5A Synthetase/RNaseL pathway exert a negative control on protein synthesis. Both of these anomalies have been demonstrated in CFS. In addition, muscle fiber atrophy and a defect in muscle energy sources need to be explored as there is disagreement whether patients with CFS show defects in mitochondrial function.

This study clearly shows that patients with CFS are limited in their physical capacities. Based on the American Medical Association Guidelines for Impairment Rating, our 55.2% of patients who had a VO2max of less than 20 mL/kg per minute correspond to class 3-4 on the disability scale, indicating moderate to severe impairment. Regardless of the cause and pathogenesis, the symptom complex labeled CFS can and does result in prolonged debilitation.

To our knowledge, this is the first study on exercise capacity in a large population of patients with CFS and sedentary control subjects. Physical capacity based on exercise tolerance is only one of a number of factors that might be considered in establishing a more global impairment rating. However, we believe it is a strong and useful tool in assessing a person’s physical capability.

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REFERENCES

Error in Figures. In the Original Investigation by De Becker et al titled “Exercise Capacity in Chronic Fatigue Syndrome,” published in the November 27, 2000, issue of the ARCHIVES (2000;160:3270-3277), incorrect figures were inadvertently submitted for Figures 1, 2, 3, and 4. The figures are reprinted correctly here.

**Figure 1.** Categorized scatterplot of the differences in workload and heart rate at the anaerobic threshold in patients with chronic fatigue syndrome (CFS) and in control female subjects. The diagonal solid line represents 95% confidence interval (regression analysis); diagonal dashed lines, 95% confidence limits (1 SD).

**Figure 2.** Categorized scatterplot of the differences in maximal workload and heart rate at the anaerobic threshold in patients with chronic fatigue syndrome (CFS) and in control female subjects. The diagonal solid line represents 95% confidence interval (regression analysis); diagonal dashed lines, 95% confidence limits (1 SD).
Figure 3. Categorized scatterplot of the differences in \( V_{\text{O}_2\text{max}} \) and heart rate at the anaerobic threshold in patients with chronic fatigue syndrome (CFS) and in control female subjects. The diagonal solid line represents 95% confidence interval (regression analysis); diagonal dashed lines, 95% confidence limits (1 SD).

Figure 4. Categorized scatterplot of the differences in exercise duration and heart rate at the anaerobic threshold in patients with chronic fatigue syndrome (CFS) and in control female subjects. The diagonal solid line represents 95% confidence interval (regression analysis); diagonal dashed lines, 95% confidence limits (1 SD).