

## Physical activity before and after exercise in women with chronic fatigue syndrome

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### Summary

We measured physical activity after strenuous exercise in 20 women with chronic fatigue syndrome (CFS), compared to 20 sedentary healthy volunteers who exercised no more than once per week. Activity was measured for 2 weeks using a portable waist-worn vertical accelerometer. After the first week of activity monitoring, all participants returned for a maximal treadmill test, followed by continued activity monitoring for the second week. Five activity measures were derived from the data: (i) average activity; (ii) total activity; (iii) duration of waking day; (iv) duration; and (v) number of daily rests. A

repeated measures ANCOVA was used to determine post-treadmill group differences accounting for pre-treadmill differences. There was a significant reduction in overall average activity after the treadmill test, with the greatest decrease on days 12 through 14. This reduction was accompanied by a significant increase in the duration of the waking day and number of daily rests. Thus, marked exertion does produce changes in activity, but later than self-report would suggest, and are apparently not so severe that CFS patients cannot compensate.

### Introduction

Chronic fatigue syndrome is a medically unexplained illness producing a 'substantial' decrease in daily activity plus a number of ancillary symptoms.<sup>1</sup> One of these symptoms is the complaint that even minimal physical exertion produces a major 'flare up' of symptoms producing even more marked limitations in activity<sup>2</sup>—with some people actually reporting an inability to get out of bed. To determine whether decreases in activity are 'substantial' and whether

the patient in fact has post-exertional fatigue requires physician judgment based on patient self-reported recall. Asking patients to compare current activity with that occurring months to years earlier is obviously a problem. This problem is compounded by the fact that complaints of problems with attention and memory are a frequent component of CFS.<sup>3</sup> An objective accurate measure of activity would help obviate these problems.

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Recording activity with an accelerometer provides such an objective measure of activity. Accelerometers have been used to measure physical activity as early as 1960, when vertical acceleration was measured while participants walked on a treadmill.<sup>4</sup> Haskell and associates<sup>5</sup> reported that physical activity motion sensors have a major use in quantifying physical activity. One accelerometer, the Caltrac, produces data that correlates well with physical activity both in controlled<sup>6</sup> and naturalistic settings.<sup>7</sup> Disadvantages of the Caltrac are its size, and that its settings can be altered. The CSA accelerometer circumvents these problems and cross-validates well with the Caltrac ( $r=0.82$ ).<sup>8</sup> Janz and associates<sup>9</sup> conducted a validation study of the CSA accelerometer with children, using heart rate as the criterion measure. The validity correlation coefficients ranged between 0.5 and 0.74. The moderate to high validity correlation and the subjects' favourable response to wearing the accelerometer supported its validity and utility as an objective method for monitoring activity in field settings. The purpose of this study was to assess physical activity using the CSA portable waist-worn accelerometer before and after a maximal exercise test, in women with CFS, compared to sedentary healthy controls.

## Methods

### Patients

CFS patients were identified from advertisements for individuals complaining of fatigue that were placed in community and support group newsletters, newspapers and from letters of request sent to surrounding primary care physicians. All interested subjects responded by telephone and were mailed initial screening forms. Responses were reviewed to determine if they met the study's initial inclusion criteria for number of symptoms, age and duration of illness. The potential subjects were given a physical examination and blood work to rule out subjects with medical causes of fatigue. They also underwent a psychiatric diagnostic interview<sup>10</sup> to exclude patients with a lifetime history of schizophrenia, bipolar or eating disorders, or a history of any DSM-III-R Axis I psychological disorder in the 5 years prior to CFS onset. Patients with substance abuse and/or alcohol abuse were excluded if this diagnosis occurred within 10 years of the onset of CFS. Other exclusion criteria were loss of consciousness in the 5 years prior to the onset of CFS, duration of illness of greater than 6 years, use of anti-hypertensive and/or tricyclic antidepressant medications, morbid obesity or hypertension. We use duration of illness as an exclusion criteria for all our studies to lessen the possibility of

contamination from extraneous variables due to prolonged illness and disability—especially in our studies of psychosocial factors in CFS. We excluded subjects taking tricyclic antidepressants, but not the new generation antidepressants due to the side-effect profile of fatigue and hypotension in the tricyclics.

Healthy subjects were recruited from advertisements in area newspapers and flyers placed in public places. Sedentary control subjects reported themselves to be in good health on medical interview, were taking no prescription medications other than birth control pills, and engaged in exercise no more than once a week. All subjects who fulfilled the above initial criteria were then enrolled in the research activities of the CFS Cooperative Research Center (CRC).

We restricted our study participants to Caucasian women to improve our group homogeneity, as Caucasians comprise 94% of our research population. As each subject was entered into the CRC, she was asked to participate in this trial. Using this strategy, we identified 40 women volunteers—20 healthy sedentary controls and 20 with physician-diagnosed CFS which fulfilled the 1988 CFS working case definition modified to include only those patients reporting a three or greater intensity on five point symptom severity scales in the month prior to recruitment. We have shown that this modification identifies a more homogeneous ill patient sample.<sup>11</sup> In order to participate in this study, patients had to be well enough to perform a maximal exercise test. Thus, bedridden and severely restricted patients did not volunteer for this study.

The CFS group ranged in age from 18 to 55 years and in their duration of illness from 8 months to 6 years (median 3.7 years). The sedentary healthy group ranged in age from 23 to 50 years. There was no significant difference in age, height and weight between the two groups. There was no significant difference in the  $\dot{V}O_2$  max (ml/kg/min) between the two groups, indicating that both groups were of similar fitness levels (See Table 1).

### Apparatus

The activity monitor (Model 7164, Computer Science and Applications, Inc., Shalimar, FL) is a small single channel device (2" × 1.5" × 0.6"; weight 1.5 oz) which contains a uniaxial accelerometer oriented in the vertical direction. The decision to use only a vertical accelerometer was based on pilot work indicating (i) that the addition of other axes of motion did not add any new information to the data and (ii) other accelerometers were not comparable in terms of durability or portability compared to the CSA device. Since vertical motion most closely represents activity requiring the greatest energy

**Table 1** Participant characteristics

Group	Age (years)	Height (cm)	Weight (kg)	VO <sub>2</sub> MAX (ml/kg/min)
CFS ( <i>n</i> =20)	33.6 (7.0)	164.4 (5.9)	66.4 (13.9)	27.2 (1.6)
Sedentary healthy ( <i>n</i> =20)	33.0 (9.0)	165 (6.9)	61.6 (12.6)	30.4 (1.0)

Data are means (SD)

expenditure, i.e. against gravity, it was the most pertinent direction of motion to evaluate with a population which complains of lack of energy. The accelerometer within the CSA device is designed to detect acceleration ranging in magnitude from 0.05 to 2 Gs with a frequency response from 0.25 to 2.5 Hz. These parameters fall into the range of normal human motion<sup>12</sup> and are designed to reject high-frequency motion such as the vibration of a lawn mower. The filtered acceleration signal is digitized and the magnitude summed over a 1 minute epoch, after which the summed value is stored in memory and the hardware integrator automatically resets itself.<sup>13</sup> The apparatus has a data storage capacity of over 22 days, and can be downloaded via an infrared reader unit to a personal computer for subsequent data analysis.

## Procedures

Subjects signed informed consent, and then received an activity monitor and waist belt one week before the treadmill exercise test. The participants were instructed to wear the activity monitor on the waistbelt at all times except while bathing or during night-time sleep. After 7 days of wearing the waist activity monitor (WAM), subjects performed a treadmill exercise test which consisted of a progressive ramping of the treadmill speed and grade for 3-min workloads until the participant could no longer continue. Each participant was encouraged to reach her age-predicted maximal heart rate which was determined by the equation  $(210 - [0.65 \times \text{age}])$ .<sup>14</sup> Following the treadmill test, the participants wore the activity monitor for an additional seven days. A prior study indicated 5–7 days of activity were needed to represent stable daily physical activity data.<sup>15</sup> The activity monitors were collected after the 14-day period.

Although all participants were asked to wear their monitor for at least 7 days before and after the treadmill test, compliance was not always 100%. Therefore it became important to assess the level and pattern of missing data. There were 21 missing days of activity from a potential 280 pre-treadmill days of activity, and 25 missing days of activity from a potential 280 post-treadmill days of activity. This translates to approximately 7.5% pre-treadmill and 8.9% post-treadmill days missing days of activity

from the potential complete data set. Missing data reduced the 560 possible daily activity days to 511.

An evaluation of the pattern of wear of the WAM indicated that the CFS and the healthy subjects respectively wore the monitor 6.6 and 6.4 days before the treadmill test and 6.3 and 6.5 days after the treadmill test. A Wilcoxon rank sum test indicated no significant difference in the number of days that the activity monitor was worn between the two groups. The reasons noted in the diary for not wearing the monitor on a given day did not differ from the pre-treadmill reasons, despite the treadmill exercise test intervention. Informal inquiry when picking up each activity monitor revealed only one case where the participant reported to be fatigued for 2 weeks after the test. Since the reasons for non-wear days were not related to the level of activity, the pattern of missing data was considered random. Therefore, a total of 511 days of activity were used for all subsequent statistical analysis.

## Data processing

The 2-week data files were broken down into single day files according to clear breaks in the data that corresponded to the sleep cycles indicated in the written diaries. Occasional blocks of time where the monitor was off as indicated in the diary, such as for a shower or swimming, were removed from the raw data. These events occurred randomly throughout both groups. The activity data were evaluated in a series of logical steps. The activity per minute was averaged for each day before and after the treadmill intervention. Because daily activity scores demonstrated marked variability and non-normal distributions, heterogeneity of variance was reduced by doing a square-root transformation of the data prior to statistical analysis.

Other measures of daily activity were derived from the original activity data. First, to determine group differences in the total amount of activity across the entire waking day, activity measures per minute were added for each day. Second, to examine group differences in the duration of activity for each day, the number of minutes of activity between waking and bed time was tallied for each day. Finally, to examine group differences in the amount of rest periods during the day, the number of continuous intervals where the WAM registered zero

was determined. In this condition, no vertical body motion exists, thus reflecting inactivity or rest. A rest was defined as any period in which no activity was recorded on the WAM for two or more consecutive minutes. The duration of each of these rest periods was recorded and analysed. Further analysis of inactivity throughout the waking day was done on the total number of rests occurring each day.

## Statistical analysis

Between-group comparisons of physical activity measured by the portable accelerometer included: (i) daily average activity level per minute; (ii) daily total activity; (iii) the total number of active minutes per day; (iv) the average duration of rest throughout the day; and (v) the number of rests throughout the day. Data were analysed using the SAS (ver. 6.11) statistical package Mixed procedure<sup>16</sup> to perform the ANOVA for repeated measures. Since the data included random missing values, the restricted maximum likelihood estimate (REML) was implemented. A favourable theoretical property of REML is that it accommodates data that are missing at random, and reduces some of the bias found in the ordinary maximum likelihood estimates.<sup>17,18</sup> A repeated measures analysis of variance (RMANOVA) was used to determine if there were differences across all 7 days prior to and after the treadmill test between the CFS and the sedentary healthy groups on each of these five activity measures. To control for any differences that might have existed prior to the treadmill testing, post-treadmill data always accounted for pre-treadmill activity using a repeated measures analysis of covariance (RMANCOVA) procedure. The average pre-treadmill activity measures were used as the covariate. The contrasts procedure<sup>16</sup> was used to compare the average activity for the first 4 days after the treadmill test to each of the post-treadmill days thereafter.

## Results

### Average daily activity

#### *Pre-treadmill*

A RMANOVA across the seven pre-treadmill days indicated a statistically significant group difference between the CFS and sedentary healthy groups ( $F = 8.94$  [1,38],  $p < 0.01$ ) with the CFS group demonstrating 15% less average activity per unit time (mean 7.3, SEM 0.2) compared to the healthy (mean 8.6, SEM 0.2). Additionally, the RMANOVA indicated a significant group-by-day linear interaction ( $F = 7.89$  [1,214],  $p < 0.01$ ) showing a significant trend toward increased activity over the one-week period with the

CFS patients but the control group remained at a stable level of activity.

#### *Post-treadmill*

After accounting for pre-treadmill differences, RMANCOVA on activity levels across the post-treadmill period indicated a significant group difference in post-treadmill daily activity ( $F = 5.07$  [1,36],  $p < 0.04$ ) with the CFS group demonstrating 10% less activity (mean 7.7, SEM 0.7) compared to the sedentary healthy group (mean 8.6, SEM 0.6). There was a significant group-by-time interaction explained by both a linear ( $F = 5.45$  [1,211],  $p < 0.03$ ) and a quadratic time effect ( $F = 6.29$  [1,211],  $p < 0.02$ ). Figure 1 expresses the post-treadmill data in terms of percent of the median pre-treadmill values. The activity data for the CFS group demonstrated a small rise in activity, followed by a drop which was maximal on the last day of data acquisition; in contrast, the healthy group showed the same small rise with no subsequent drop.

The CFS group showed a significant decrease in activity per unit time ( $F = 11.3$  [1,100],  $p < 0.0002$ ) on the average of days 12, 13, and 14 compared to the first four post-treadmill days during which period activity had not significantly changed from pre-treadmill values. The healthy group did not significantly change its activity levels for any of the days after the treadmill test. At its nadir, CFS activity was 30% decreased compared to the day before the treadmill test, and the healthy group exhibited virtually no decrease on this same day. The decrease in average activity exhibited by the CFS group on days 12 through 14 was significantly different from that shown by the sedentary controls ( $F = 5.36$  [1,209],  $p < 0.03$ ; see Figure 1).

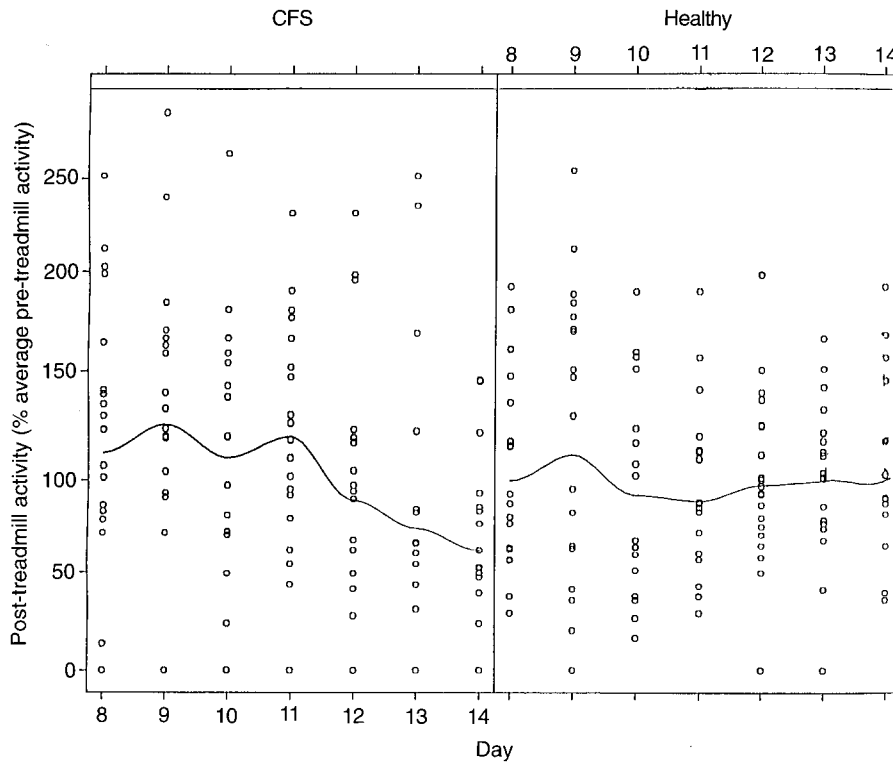
### Total daily activity

A RMANOVA across the pre-treadmill period revealed no significant group or time effects. A RMANCOVA across the post-treadmill period revealed no significant group or time effects (see Figure 2).

### Length of active day

#### *Pre-treadmill*

A RMANOVA revealed no significant group effect. However, a significant group-by-day interaction was found ( $F = 7.27$  [1,216],  $p < 0.009$ ) indicating that the active day length of the CFS group but not the healthy controls declined over time (CFS: mean 746 min, SEM 12 min; healthy: mean 833 min, SEM 7 min). Thus, the day length of the CFS group was approximately 1.5 h or 10% shorter than that of sedentary healthy subjects.



**Figure 1.** Percent change from mean pre-treadmill activity after treadmill testing with the CFS group depicted on the left and the healthy subjects on the right. Each subject's data for each of the 7 days of data collection are depicted and a trend line is fitted by a local regression method.<sup>24</sup> Note that the activity of the CFS group decreases starting on day 12 while that of the healthy group remains unchanged.

### Post-treadmill

After accounting for the pre-treadmill differences, RMANCOVA revealed a significant group effect ( $F = 4.35$  [1,37],  $p < 0.05$ ), with the CFS group having 9% shorter average day lengths (mean 751 min, SEM 9.7) compared to the healthy group (mean 825 min, SEM 8.6). There was also a significant group by time interaction ( $F = 4.79$  [1,213],  $p < 0.04$ ) manifested by a slight increase in duration of active periods for the CFS subjects as contrasted with a decrease in active periods for the control subjects over the same time (see Figure 3). At its peak on day 12, the CFS group had a 13% longer day length (796 mins) than the day before the treadmill test (691 mins). At its nadir on day 14, the control group was 11% lower (779 mins) than the day before the treadmill test (889 mins).

### Daily rests

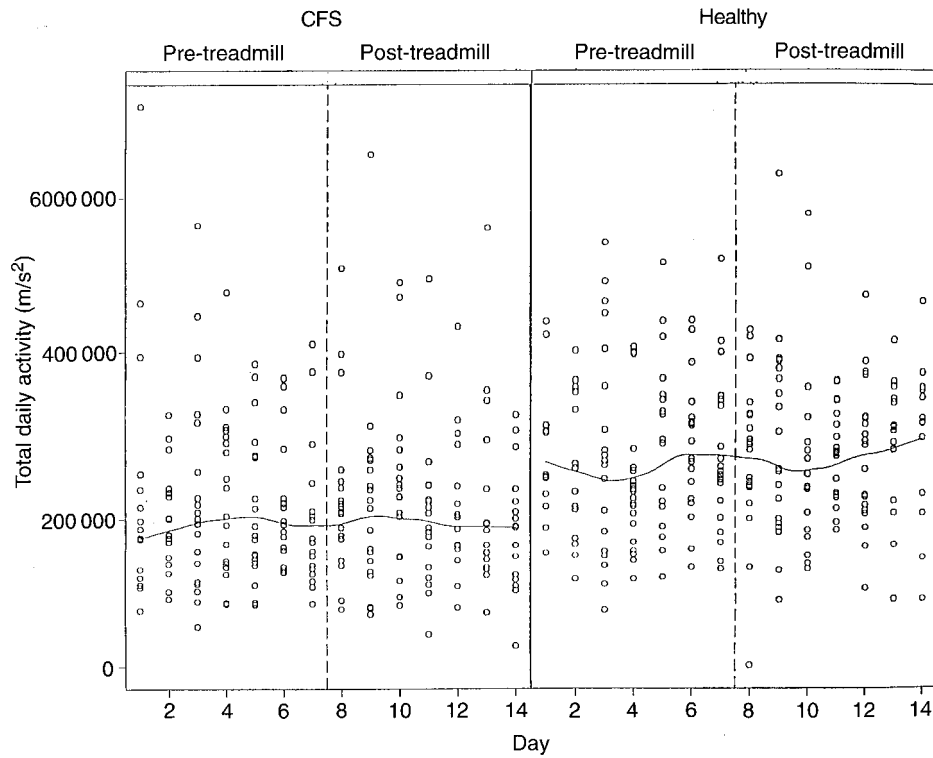
#### Pre-treadmill

A RMANOVA indicated no significant group or time effects in the average duration of the daily rest bouts. There was no significant group effect in the number of rest bouts per day, but there was a significant group-by-time interaction ( $F = 6.32$  [1,215],  $p < 0.02$ ). The CFS group showed a decline in the

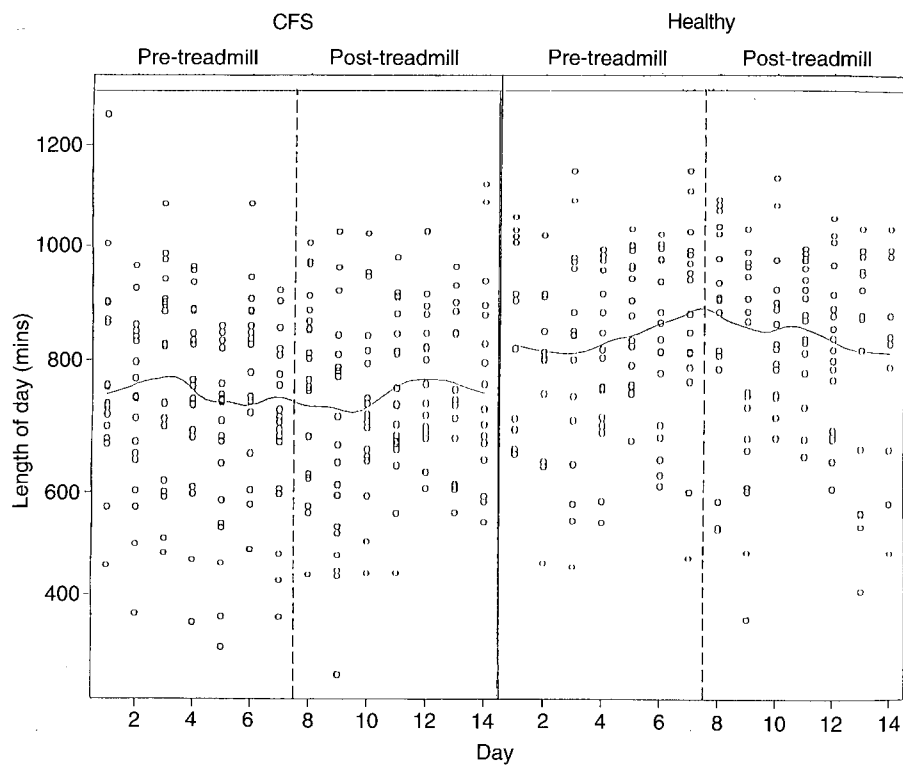
number of rests per day as they approached the treadmill test day, while the healthy group maintained a relatively constant number of rests per day. At its nadir, the CFS group reduced their number of rests per day by 23% over the course of the pre-treadmill period, while the healthy group actually increased their rests slightly (8%).

#### Post-treadmill

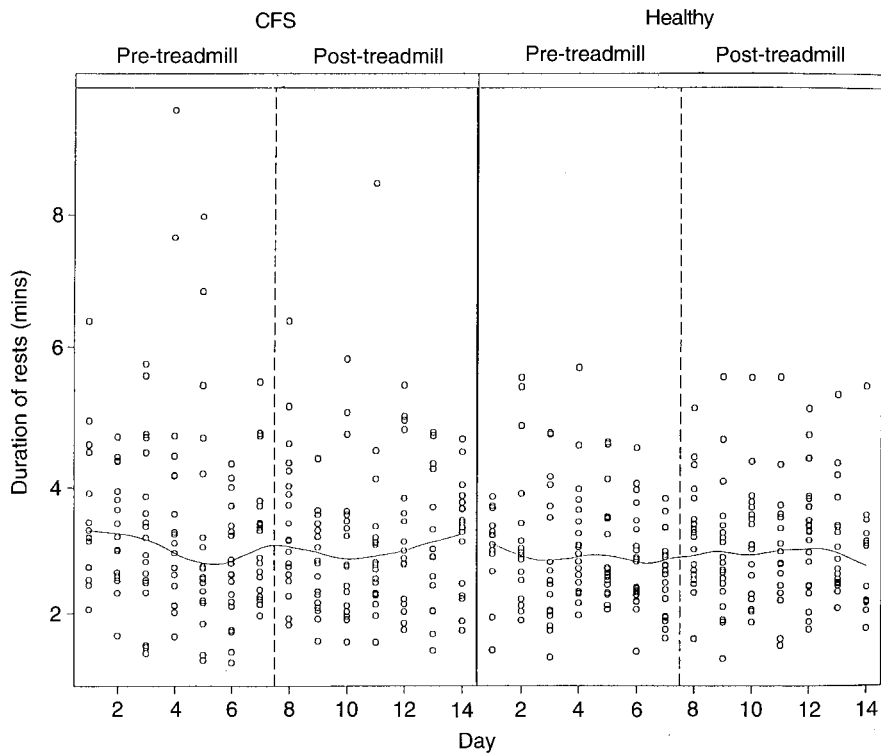
After accounting for pre-treadmill differences, RMANCOVA revealed no group or time effects on the duration of the consecutive rest periods (See Figure 4). A similar analysis on the number of daily rests, after accounting for the pre-treadmill differences, revealed a significant group ( $F = 5.77$  [1,37],  $p < 0.03$ ) and group-by-time interaction ( $F = 5.5$  [1,214],  $p < 0.03$ ; see Figure 5). At its peak, the CFS group increased their number of rests by 26.5%, whereas the healthy group slightly decreased their number of rests (1.6%). The CFS group showed a significant increase ( $F = 7.52$  [1,100],  $p < 0.008$ ) in the number of daily rests on days 12, 13 and 14 compared to the first four days, during which time the number of rests did not significantly change from pre-treadmill rates. The number of rests for the healthy group did not significantly change after treadmill testing (See Figure 5).



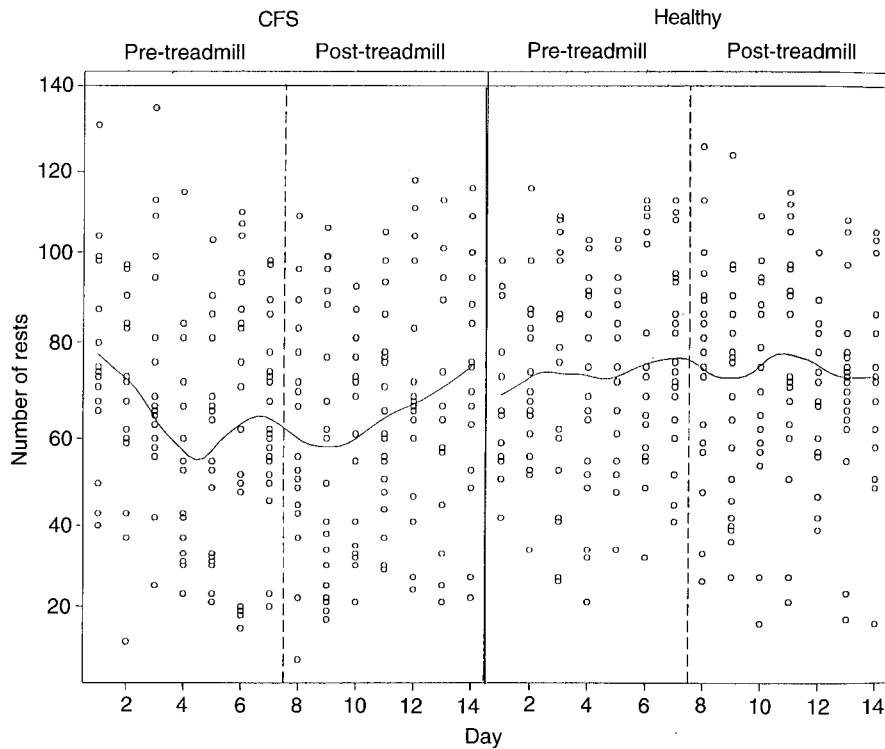
**Figure 2.** Median total daily activity (summed accelerations over the waking day) for the CFS and healthy subjects (left and right panels, respectively) before and after the treadmill test; time of exercise test depicted by the dashed vertical lines. Each subjects data for each of the 14 days of data collection are depicted and a trend line is fitted by a local regression method.<sup>24</sup>



**Figure 3.** Average duration of waking time to bedtime for CFS and healthy groups (left and right panels, respectively); time of exercise test depicted by the dashed vertical lines. Each subject's data for each of the 14 days of data collection are depicted and a trend line is fitted by a local regression method.<sup>24</sup>



**Figure 4.** Average duration of rests or consecutive minutes where activity monitor recorded fewer than two summed accelerations of physical activity throughout the waking day for CFS and healthy groups (left and right panels, respectively); time of exercise test depicted by the dashed vertical lines. Each subject's data for each of the 14 days of data collection are depicted, and a trend line is fitted by a local regression method.<sup>24</sup>



**Figure 5.** Average number of rests where activity monitor recorded consecutive bouts of summed accelerations of physical activity less than two throughout the waking day for the CFS and healthy groups; time of exercise test depicted by the dashed vertical lines. Each subject's data for each of the 14 days of data collection are depicted, and a trend line is fitted by a local regression method.<sup>24</sup>

## Discussion

The results of this study indicate that the effect of a maximal exercise test does not produce immediate dramatic effects on recorded average activity or on the number of daily rests for the CFS group, but does so 5 days later. An unexpected outcome was that neither total daily activity nor duration of rests changed following maximal treadmill testing. This outcome is quite different from that predicted by the fear avoidance model of post-exertional fatigue in CFS and thus does not support that model.

Thus, the data do not support the frequent report of CFS patients that exertion puts them to bed 1–2 days later.<sup>19</sup> This is important because maximal exercise tests are often done to track studies of gentle physical conditioning. It may be that the brief aerobic exertion is not what produces their increase in fatigue reported by CFS patients, but that an extended submaximal exercise test might produce this outcome. However, our own ongoing work treating CFS by gentle physical conditioning along with the work of Fulcher and White<sup>20</sup> does not support this possibility either. In that study, participants only rarely reported a severe increase in symptoms following submaximal exertion.

Another explanation is that the CFS patient somehow misinterprets the way she feels after exertion. Although the duration of rest does not change after exertion, the CFS patient does rest more frequently after strenuous exercise. CFS patients may interpret their need for more, albeit brief, rests, as decreased activity after exertion. There may also be a problem with the patient's perception of post-exertional fatigue. In our last study<sup>20</sup> when a simple Likert scale of fatigue was administered after the same treadmill exercise test, patients reported a significant increase in fatigue which remained for a 2-week period. When a more complex questionnaire which had questions about fatigue embedded with questions about other feelings was administered 4 days after the treadmill test, the same significant increase was not seen. Thus, the patients' expectations that they should be fatigued following exertion rather than a striking increase in fatigue due to exertion may be responsible for this apparent discrepancy.

Another possibility may relate to patients mislabeling the time of their diminished activity. Patient self-report is that this occurs 1–2 days after the end of exertion. Average activity did fall, but not within this time frame. Instead it fell 5–7 days after the end of exertion. At this same time, the number of rests for the CFS patients was also increasing. Thus, our results showing a 30% decrease in average activity after exertion support the patient self-report of an activity decrease, although it is delayed beyond the point that the patient usually reports. It is possible that CFS patients recall that this occurs several days

after exertion but instead are incorrectly remembering the time that the decrease in activity actually begin. These data support the need for further research on post-exertional fatigue using objective measures such as the actigraph rather than relying on patient self-report.

It is important to point out that despite both more rests and a decrease in average activity on days 5 through 7 following exertion for the CFS group, total daytime activity did not change at this time. This indicates that CFS patients appear to compensate for post-exertional consequences by lengthening their active period. This trend toward a longer active period in the latter half of the post-treadmill week is apparent in Figure 3. The fact that CFS patients can compensate for reduced average activity by remaining active for longer periods implies that the delayed effects of strenuous exercise on activity are not dangerous to the patient. Thus, these data support patient self-report of diminished activity but do not provide objective evidence for the additional self-report that these effects are extreme.

We must point out a number of shortcomings with the nature of the activity data collected. First, it was expected that a one-week baseline period would be enough to generate stable baseline data. While that was true for the healthy controls, it was not always true for the CFS patients. Whether this baseline variability represented anxiety concerning the upcoming treadmill test or variability of activity innate to CFS is not clear. This baseline variability may provide objective support for the clinical impression that patients with CFS tend to do too much on one day, causing them to be far less active the next day, thus having a 'roller-coaster' effect on activity. However, this baseline instability may have reduced our ability to understand the effects of exertion on measures of activity, since our statistical analysis was done after accounting for average baseline data. Therefore, subsequent studies of activity in CFS patients need to evaluate baseline activity for longer than 7 days to either improve stability of the baseline activity measures or to document any inherent variability in CFS activity which in itself may be meaningful.

A second problem may lie in our decision to allow subjects to remove the WAM at bedtime. Doing this prevented us from doing an analysis on continuous data to test the hypothesis that CFS fatigue may be due to loss of entrainment of biological rhythms. We are presently planning a study to allow the collection of around-the-clock data before and after exertion.

A third shortcoming results from our inability to match the baseline activity levels of our controls to our CFS patients despite our using sedentary controls. They exhibited 15% more average activity and a 10% longer average day length. It is interesting to point out that the small baseline difference is similar

to the small differences in aerobic capacity between patients and controls which we have reported following maximal exertion.<sup>21</sup>

It is important to understand the cause of this delayed decrease in activity. Although cytokine release following exercise could be responsible, exertion-induced changes are self-limited and return to normal 1–2 days after exercise.<sup>22</sup> It is possible that CFS patients do not have this normal response, and that their cytokines remain elevated for longer periods of time than in controls. Studies of muscle bioenergetics<sup>23</sup> using magnetic resonance spectroscopy before and after a maximal treadmill test in CFS eliminate muscle microtrauma as an explanation. Muscle metabolism did not change from baseline following maximal exertion. Another possibility is that strenuous exercise further disrupts sleep in CFS patients—an effect which may accumulate over days leading to the delayed appearance of increased fatigue. It is obvious that further research confirming exertion-induced alterations in activity is important to replicate our findings and to extend them to better comprehend the CFS symptoms of post-exertional malaise and finally to understand its genesis.

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## References

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: A comprehensive approach to its definition and study. *Ann Int Med* 1992; **121**:953–69.
2. Komaroff AL, Buchwald D. Symptoms and signs of chronic fatigue syndrome. *Rev Infect Dis* 1991; **13**:S8–11.
3. Johnson SK, Lange G, DeLuca J, Korn LR, Natelson B. The effects of fatigue on neuropsychological performance in patients with chronic fatigue syndrome, multiple sclerosis and depression. *Appl Neuropsychol* 1997; **4**:145–53.
4. Cotes JE, Meade F. The energy expenditure and mechanical energy demand in walking. *Ergonomics* 1960; **36**:97–119.
5. Haskell WL, Leon AS, Caspersen CJ, Froelicher VF, Hagberg JM, Harlan W, Holloszy JO, Regensteiner JG, Tompson PD, Washburn RA, Wilson PWF. Cardiovascular benefits and assessment of physical activity and physical fitness in adults. *Med Sci Sports Exerc* 1991; **24**(Supplement):S201–19.
6. Klesges RC, Klesges LM, Swenson AM & Pheley AM. A validation of two motion sensors in the prediction of child and adult physical activity levels. *Am J Epidemiol* 1985; **122**:400–10.
7. Washburn RA, Janey CA, Fenster JR. The validity of objective physical activity monitoring in older individuals. *Res Q Exerc Sport* 1990; **61**:114–17.
8. Melanson EL, Freedson PS. Validity of the Computer Science and Applications, Inc. (CSA) activity monitor. *Med Sci Sports Exerc* 1995; **27**:934–40.
9. Janz KF, Cassady SL, Barr RN, Kelly JM. Monitoring exercise in children and adolescents with Cystic Fibrosis: Validation of the CA accelerometer. *Cardiopulm Phys Ther* 1995; **6**:3–8.
10. Marcus S, Robins LN, Bucholz K. *Quick Diagnostic Interview Schedule 3R*, Version 1. St. Louis MO, Washington University School of Medicine, 1990.
11. Natelson BH, Johnson SK, DeLuca J, Sisto S, Ellis SP, Hill N, Bergen MT. Reducing heterogeneity in the chronic fatigue syndrome: A comparison with depression and multiple sclerosis. *Clin Infect Dis* 1995; **21**:1204–10.
12. Magyar GAL, Westerterp KR, Verhoeven FMH, Koper HBM, ten Hoor F. Methods to assess physical activity with special reference to motion sensors and accelerometers. *IEEE Trans Biomed Eng* 1991; **38**:221–9.
13. Tryon WW, Williams R. Fully proportional actigraphy: A new instrument. *Behav Res Meth*, 1996; **28**:392–403.
14. Londeree BR, Moeschberger ML. Effect of age and other factors on maximal heart rate. *Res Q Exerc Sport* 1982; **00**:297.
15. Washburn RA, LaPorte RE. Assessment of walking behavior: Effect of speed and monitor position on two objective physical activity monitors. *Res Q Exerc Sport* 1988; **59**:83–5.
16. SAS Institute Inc. *SAS/STAT Software Changes and Enhancements, through Release 6.11*. Cary NC, SAS Institute, 1996:596.
17. Little RJA, Rubin DB. *Statistical Analysis of Missing Data*. New York, John Wiley & Sons, 1987.
18. Little RJA. Modeling the drop-out mechanism in repeated measures studies. *Am Statist Assoc* 1995; **90**:1112–21.
19. Wilson A, Hickie I, Lloyd A, Wakefield D. The treatment of chronic fatigue syndrome: Science and speculation. *Am J Med* 1994; **96**:544–50.
20. Fulcher KY, White P. Randomised controlled trial of graded exercise in patients with chronic fatigue syndrome. *Br Med J* 1997; **31**:1647–52.
21. Sisto SA, LaManca JJ, Cordero DL, Bergen MT, Drastal S, Boda WL, Tapp WN, Natelson BH. Metabolic and cardiovascular effects of a progressive exercise test in patients with chronic fatigue syndrome. *Am J Med* 1996; **100**:634–40.
22. Lloyd A, Gandeia S, Brockman A, Hales J, Wakefield D. Cytokine production and fatigue in patients with chronic fatigue syndrome and healthy control subjects in response to exercise. *CID* 1994; **18**(Suppl 1):S142–6.
23. McCully KK, Natelson BH, Iotti S, Sisto SA, Leigh JS. Reduced oxidative muscle metabolism in chronic fatigue syndrome. *Muscle Nerve* 1996; **19**:621–5.
24. Cleveland WS, Grosse E, Shyu WM. Local Regression Models. In: Chambers JM, Hastie TJ, eds. *Statistical Models in S*. Pacific Grove CA, Wadsworth Brooks/Cole Advanced Books & Software, 1991: 309–76.