RELIABILITY OF PHYSIOLOGICAL, PSYCHOLOGICAL AND COGNITIVE VARIABLES IN CHRONIC FATIGUE SYNDROME AND THE ROLE OF GRADED EXERCISE.

Karen E. Wallman, Alan R. Morton, Carmel Goodman and Robert Grove

School of Human Movement and Exercise Science, The University of Western Australia, Crawley, Western Australia

ABSTRACT

The objective of this study was to assess variability in symptoms and physical capabilities in chronic fatigue syndrome (CFS) participants both before and after a graded exercise intervention. Sixty-one CFS subjects participated in a 12-week randomized controlled trial of either graded exercise (n = 32) or relaxation/stretching therapy (n = 29). Specific physiological, psychological and cognitive variables were assessed once weekly over a four-week period both prior to and after the intervention period. All scores were assessed for reliability using an intraclass correlation coefficient (ICC). Apart from mental and physical fatigue, baseline ICC scores for all variables assessed were moderately to highly reliable, indicating minimal variability. Baseline scores for mental and physical fatigue were of questionable reliability, indicating a fluctuating nature to these symptoms (R1 = 0.64 and 0.60, respectively). Variability in scores for mental fatigue was reduced after graded exercise to an acceptable classification (R1 = 0.76). Results from this study support a variable nature to the symptoms of mental and physical fatigue only. Consequently, in order to more accurately report the nature of mental and physical fatigue in CFS, future studies should consider using repeated-measures analysis when assessing these symptoms. Graded exercise resulted in the reclassification of scores for mental fatigue from questionable to acceptable reliability.

KEY WORDS: Fluctuating symptoms, repeated measures, single session measures, repeatability.

INTRODUCTION

The term chronic fatigue syndrome was chosen by the Centers for Disease Control and Prevention (CDC; Atlanta, USA) to describe a syndrome that consisted of chronic debilitating fatigue, which could not be explained by any known chronic medical or psychological condition (Holmes et al., 1988). As a result of this debilitating fatigue, it is not uncommon for sufferers to also complain of depression, anxiety and a reduced physical capacity (Wessely and Edwards, 1993). Attempts to determine the etiology for this disorder have involved intensive research without the benefit of conclusive results. To date there is no known cure.

An intriguing aspect to chronic fatigue syndrome (CFS), that has important research implications, is that sufferers typically report a fluctuating nature to their symptoms and physical capabilities (Evengard et al., 1999; Wilson et al., 1994). This is represented by periods of wellness, where near normal activity levels are often resumed, and then periods of relapse that often requires bed rest (Evengard et al., 1999; Wilson et al., 1994). Unfortunately, little research has been undertaken to...
date in order to investigate this feature of CFS, yet
discard to account for possible variation in
symptoms and physical capabilities when
conducting studies in this population can lead to the
reporting of results that do not accurately reflect the
ture nature of CFS, nor the efficacy of an
intervention. This conjecture is supported by various
researchers who note that the reporting of single-
session measures may yield inconclusive results, as
levels of fatigue and effort can vary over extended
periods of time (Fuentes et al., 2001; Gantz and
Holmes, 1990; Kane et al., 1997). This is
particularly pertinent if a study cohort does not meet
power requirements and where symptom
fluctuations in a small group of subjects may
significantly influence research outcomes. Use of
single-session measurements in order to assess
calibration and post-intervention variables is common
in CFS research (Fulcher and White, 1997; Powell et
al., 2001; Weardon et al., 1998), as are small cohorts
(Cannon et al., 1999; Paul et al., 1999; Clapp et al.,
1999). To date, studies that have assessed the
fluctuating nature of CFS have reported symptom
variation over time periods ranging from 24 hours to
3.5 years (Fuentes et al., 2001; Heinman, 1995; Hill
et al., 1999; Cabane et al., 2000). These results
suggest that single-session assessment of variables
previously shown to be reliable may not be
sufficient in a CFS population.

Reliability can be referred to as the amount of
variation that occurs in results between trials
(MacDougall et al., 1991), or the consistency of
measurements from trial to trial (Safrit and Wood,
note that the term reliability is interchangeable with
the terms ‘repeatability’, ‘reproducibility’, ‘stability’,
‘agreement’ and ‘concordance’, while the phrase
‘stability reliability’ is defined specifically as
relating to the day-to-day variability in
measurements. Atkinson and Nevill (1998) further
note that in some circumstances more time than a
day may be needed between measurement sessions
in order to allow for recovery from exercise tests.

If there is a fluctuating nature to symptoms
and capabilities in CFS, then graded exercise may
have a role in reducing this variability. Symptoms
and physical capabilities in CFS sufferers have
consistently been shown to be improved by the use
of graded exercise therapy (Fulcher and White,
1997; Powell et al., 2001; Wallman et al., 2004;
Weardon et al., 1998). It is therefore plausible to
postulate that graded exercise may also reduce the
range in any variation found in these symptoms and
physical capacities.

The aim of our study was twofold. Firstly, we
aimed to assess the stability and reliability of scores
recorded for specific physical, psychological and
cognitive variables that were measured once a week
over a four-week period in a CFS population.
Measurements were made on a weekly rather than a
daily basis in order to allow CFS participants time to
recover fully from their previous exercise session.
Reliability scores were then categorised according to
guidelines proposed by Vincent (1995) as being
either highly reliable, moderately reliable or of
questionable reliability (see the statistical procedures
section). A second aim of our study was to
determine whether a twelve-week program of graded
exercise therapy was capable of reducing any
variability found in any of the measures analysed
during the initial assessment. It was hypothesized
that all baseline variables assessed would be of
questionable reliability (i.e. highly variable) and that
a twelve-week graded exercise program would
reduce this variability, resulting in the
reclassification of intraclass correlation coefficient
(ICC) scores to more reliable categories.

METHODS

Eighty-two chronic fatigue syndrome participants
(aged between 16-74 years) were recruited from
advertisements placed in local newspapers and from
notices placed in medical surgeries. Prior to
participation in this study, written confirmation of a
CFS diagnosis was required from each subject’s
medical doctor. To receive a CFS diagnosis,
participant’s needed to meet the working case
definition of CFS as defined by Fukuda et al. (1994).
This definition requires two major criteria and four
of eight minor criteria to be met. The major criteria
consist of the existence of severe fatigue that persists
for six months or longer and that cannot be
explained by any other chronic medical or
psychological disorder. The minor criteria consist of
a variety of minor symptoms that include impaired
memory, sore throat, tender lymph nodes, muscle
pain, multi-joint pain, new headaches, unrefreshing
sleep and post-exceptional malaise. This
requirement resulted in 14 participants being
excluded due to non-compliance or for not meeting
the CFS criteria. The remaining 68 patients were
randomized to a graded exercise or relaxation/
flexibility intervention. Randomization involved the
use of a random number table and was performed by
an independent investigator. Six participants
withdraw from the study prior to baseline testing for
personal reasons, while one participant was unable
to perform the cycle test. This left 32 CFS
participants in the graded exercise group (27 females
and 5 males), and 29 CFS participant in the
relaxation/flexibility group (20 females and 9 males;
refer Figure 1). These subjects participated in all
testing sessions held prior to and post the
intervention. All testing sessions were performed in a university performance laboratory. Participants taking medication needed to have been on this medication for at least six weeks prior to the commencement of baseline trials, while changes made to existing medication during the trials resulted in the deletion of the participant’s data prior to analysis. Ethics approval for this project was granted by the University of Western Australia Human Research Ethics Committee, and all participants completed consent forms prior to entering the trials.

Participants were required to attend weekly testing sessions that were held at the same time and on the same week day over a four-week period, both before and after the 12-week intervention program. The same exercise physiologist conducted all tests. On arrival for the first testing session, age, height and illness duration were recorded for all participants.

In order to encourage more incapacitated CFS sufferers to participate in our study, as well as increase the likelihood of participants returning for repeat testing, exercise testing involved a sub-maximal cycle test called the Aerobic Power Index test (Telford et al., 1989). This test is a modification of the PWC_{170} (physical work capacity at a heart rate of 170 bpm; Wahlund, 1948) exercise test and has been shown to be reliable in a CFS population (intraclass correlation coefficient = 0.97 which equated to high reliability; Wallman et al., 2003).

Prior to the commencement of the first testing session, a target heart rate (THR) was determined based on the formula: THR = 220 – age x 0.75 (Telford et al., 1989). Additionally, individual body-mass was recorded prior to each exercise test using Sauter scales (August Sauter GmbH D-7470 Albstadt 1 Ebingen, West Germany). Participants were then fitted with a Polar Beat HR monitor (Polar Electro Oy, Kempele, Finland), and seated on a front-entry ExerTech Ex-10 cycle ergometer (Repco Cycle Company, Huntingdale, Victoria). Seat height was adjusted and recorded along with resting HR. The exercise protocol required participants to pedal at a rate of 25 Watts (W) for one minute, with this rate increasing by 25 W every subsequent minute. The exercise test was terminated at the end of the minute that the individual THR was reached and an interpolation procedure (as described in Telford et al., 1989) was used in order to equate individual

Figure 1. Diagrammatic overview of the study protocol.
THR with the power output (W·kg⁻¹) achieved. If a participant was unable to reach their individual THR, then the Watts achieved during the last full minute of exercise were recorded as peak W·kg⁻¹. Heart rate was recorded at the end of each minute of the cycle test, while ratings of perceived exertion (RPE), as measured by the Borg scale (Borg, 1982), was recorded 55 seconds into each minute of the exercise test. A similar interpolation procedure to that used to determine power output at THR was employed to determine RPE, oxygen uptake (ml·kg⁻¹·min⁻¹) and respiratory exchange ratio (RER) values that equated to each individual’s THR. Reliability of RPE and oxygen uptake (ml·kg⁻¹·min⁻¹) values recorded during this exercise test have been previously demonstrated in a CFS population (ICC = 0.87 and 0.91, which equated to moderate and high reliability respectively; Wallman et al., 2003).

During the exercise test, oxygen consumption was analysed by a metabolic cart which consisted of a computerised on-line system. The volume of inspired air was analysed by a Morgan Ventilometer Mark II 225A (P.K. Morgan, UK), while expired air was continuously sampled and recorded every 15 seconds by Applied Electrochemistry S-3A O₂ and CD-3A CO₂ analysers (Pittsburg, PA, USA). The Morgan ventilometer and the O₂ and CO₂ sensors were calibrated prior to and after each test. All data were corrected for any gas or ventilatory drift. Analysis of data involved averaging each minute of data and then assessing the last two minutes of this data.

Current activity levels were assessed using the Older Adult Exercise Status Inventory (OA-ESI; O’Brien-Cousins, 1996). The OA-ESI is a seven-day self-report inventory that assesses the frequency, duration, and level of intensity of a wide range of work and physical activities that are commonly undertaken by people both young and old. Test-retest reliability scores from two separate studies for the OA-ESI were r = 0.756 and r = 0.771, while concurrent validity was determined by examining the correlations of weekly exercise with other previously validated activity indicators, and resulted in scores that ranged from r = 0.411 to r = 0.491 (O’Brien-Cousins, 1996).

Mental and physical fatigue were assessed using the Chalder Fatigue scale (an 11-item, self-report scale; Chalder et al., 1993). Split half reliability studies resulted in r = .861 and r = .847 (n = 274), while validation coefficients for the original 14-item Chalder fatigue scale resulted in scores of 75.5 for sensitivity and 74.5 for specificity (Chalder et al., 1993). As a consequence of this result, three items were eliminated from the Chalder fatigue scale leaving 11 items, which resulted in a Cronbach’s alpha for the revised version of 0.89 (Chalder et al., 1993). The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) is a 14-item self-report questionnaire used to rate anxiety and depression levels. Reliability, validity and psychometric properties have been established for HADS (Zigmond and Snaith). Both questionnaires required participants to rate how they felt during the previous week, including the day of testing.

Cognitive functioning was assessed using a computerised version of the modified Stroop Color Word test (MacLeod, 1991). This visual attention test assesses the level of interference caused by irrelevant stimuli. Participants were required to complete two levels of the test that differed by speed of presentation of the stimuli. Only the second and more difficult level (requiring 95 responses in a two-minute time period) was included for analysis, as the first level served as a warm-up session. Scoring was based on the number of correct responses given.

Initial exercise duration was based upon each participant’s current activity level and ranged from 5-15 minutes, while exercise intensity (HR beats per minute·bpm⁻¹) was based upon the mean HR value (bpm) achieved midpoint during the sub-maximal exercise tests. Each participant was supplied with a Polar HR monitor in order to assist them attain the required HR intensity. Graded exercise was aerobic in nature and consisted of swimming, cycling or walking. Exercise was home-based and was attempted every second day, unless a relapse occurred. If a relapse occurred, then participants were advised either to avoid exercise or to reduce the duration and/or intensity of the exercise until the participant felt that they could recommence the prescribed program again. Participants were supplied with a small laminated Borg scale and were required to rate their sense of effort on completion of each exercise session. Details relating to HR, RPE and duration of each exercise session were recorded in a diary by the participant. Every second week, participants were contacted by phone in order to review their progress and to determine the duration of the exercise session for the next fortnight. If RPE values recorded over the fortnight were either stable or decreasing, then exercise duration was increased by approximately five minutes for the following fortnight. When exercise duration reached 30 minutes, then intensity was increased by raising the target heart rate by approximately two bpm each month.

Relaxation/flexibility therapy was used in this study as a non-exercise control intervention. Participants in this group were required to listen to a 20 minute relaxation tape and to perform simple stretching exercises every second day over 12 weeks. The number of stretches performed increased gradually each fortnight from an initial number of 4
to a total of 20 in week ten. All participants kept a diary recording details of their sessions. Every second week, participants were contacted by phone in order to review their progress and to discuss the stretching prescription for the following fortnight.

The same exercise physiologist worked with both groups and a concerted effort was made in order to spend the same amount of time on the phone to all participants in both therapies. Participants participating in relaxation/stretching were asked not to participate in any extra physical activity while they were enrolled in the study.

Statistical analyses
An independent samples t-test was used in order to compare age, height, body-mass, activity levels, and illness duration between the two groups. An intraclass correlation coefficient (ICC; Winer, 1971) was employed as the primary outcome measure in order to assess the variability of data collected weekly over the four-week periods, both before and after the intervention. According to Vincent (1995), an ICC is the most appropriate method for assessing the reliability of repeated measures as an ICC is a univariate statistic that is sensitive to changes in both the order and the magnitude of these repeated values. Additionally, an ICC is the recommended method for assessing the reliability of physiological measures by the Australian Institute of Sport Laboratory Standards Assistance Scheme. Intraclass correlation coefficient values were calculated using Version 11 of the Statistical Package for the Social Sciences (SPSS) and incorporated an ANOVA. Classification of reliability for physiological and cognitive measures followed the guidelines proposed by Vincent (1995), with $R_1$ (ICC reliability) scores above 0.90 categorized as highly reliable, values between 0.80 and 0.89 considered as moderately reliable, while values below 0.80 were considered to be of questionable reliability. Further to this, ICC values below 0.70 for the self-report measures were considered to be of questionable reliability (Vincent, 1995).

RESULTS
Independent sample t-tests confirmed no significant differences between the two groups for age ($p = 0.45$), height ($p = 0.37$), body-mass ($p = 0.76$), current activity levels ($p = 0.67$), and length of illness ($p = 0.92$). On completion of the trials, participants from both groups reported that there were no adverse events associated with either intervention.

Baseline and post-intervention data for both groups can be found in Table 1. Baseline ICC scores were moderately to highly reliable (indicating minimal variability) for all variables assessed, except for scores for mental and physical fatigue, which were of questionable reliability. Post-intervention ICC scores for resting variables were similar to baseline scores for both groups in that scores for HR and systolic blood pressure (SBP) were rated as highly reliable, while

| Table 1. Intraclass Correlation Coefficient (ICC) results at baseline and after interventions. |
|---------------------------------------------------------------|----------------|----------------|----------------|
|                                                               | Baseline $R_1$ | Post-exercise $R_1$ | Post relax/stretch $R_1$ |
|                                                               | (n = 61)       | (n = 32)          | (n = 29)         |
| **Resting Variables**                                         |                |                  |                  |
| Heart Rate                                                   | .91            | .93              | .96              |
| Systolic Blood Pressure (SBP)                                | .90            | .89              | .90              |
| Diastolic Blood Pressure (DBP)                               | .87            | .86              | .85              |
| **Exercise Test Variables**                                  |                |                  |                  |
| Peak $W\cdot kg^{-1}$ at or before THR                       | .97            | .98              | .97              |
| RPE at the end of the first minute of the ET                 | .84            | .92              | .92              |
| Final RPE/peak $W\cdot kg^{-1}$ at or before THR            | .92            | .90              | .92              |
| Peak oxygen uptake (ml·kg$^{-1}$·min$^{-1}$)                | .96            | .98              | .97              |
| Respiratory Exchange Ratio                                   | .82            | .86              | .78              |
| **Psychological Variables**                                  |                |                  |                  |
| Depression                                                   | .89            | .95              | .89              |
| Anxiety                                                      | .88            | .95              | .94              |
| Mental fatigue                                               | .64            | .76              | .68              |
| Physical fatigue                                             | .60            | .67              | .62              |
| **Cognitive Variable**                                       |                |                  |                  |
| Stroop Color Word Test                                       | .88            | .93              | .92              |
| **General**                                                  |                |                  |                  |
| Activity levels                                              | .93            | .93              | .94              |

THR = target heart rate, RPE = rating perceived exertion, ET = exercise.
scores for diastolic BP were moderately reliable. In relation to the exercise test, post-intervention ICC scores for peak oxygen uptake, peak RPE/peak W·kg⁻¹, and peak power (W·kg⁻¹) were all similar to baseline values (i.e. highly reliable), except for ICC scores for RPE recorded at the end of the first minute of exercise, which improved from moderately to highly reliable for both groups after the intervention. Post-intervention reliability scores for respiratory exchange ratio were similar to baseline values for the exercise group (i.e. moderately reliable), yet changed from moderately reliable to that of questionable reliability in the relaxation/stretching group.

In relation to psychological variables, scores for anxiety and depression improved from moderately to highly reliable in the exercise group after the intervention. Post intervention scores for anxiety also improved from a moderate to a highly reliable ranking for the relaxation/stretching group, however reliability scores for depression in this group did not change over the course of the therapy. Additionally, while reliability scores for mental fatigue were similar to baseline values after relaxation/stretching therapy (i.e. of questionable reliability), reliability scores for this symptom increased by 0.12 in the exercise group resulting in an acceptable classification. Post-intervention ICC scores for physical fatigue were still highly variable in both groups (i.e. of questionable reliability).

Post-intervention scores achieved on the cognitive test improved in both groups from moderately to highly reliable, while post-intervention scores for activity levels were similar to baseline values and remained classified as highly reliable.

**DISCUSSION**

Chronic fatigue syndrome sufferers commonly report a variable nature to their symptoms and physical capabilities, however to date there have been few studies that have investigated this proposed phenomena. In order to accurately assess interventions and report results in CFS studies, this area needs further examination. Our study investigated symptom variability in specific physiological, psychological and cognitive variables that were assessed weekly over a four-week period, both before and after a graded exercise intervention. All instruments used to assess these variables had been previously shown to be reliable. While it was hypothesised that all baseline variables would be found to be of questionable reliability, results demonstrated that this was only true for scores for mental and physical fatigue. High variability in scores for mental and physical fatigue also supports previous studies that reported a fluctuating nature to the symptom of fatigue in CFS participants (Fuentes et al., 2001; Hill et al., 1999; Cabane et al., 2000). Causes proposed as the basis for high symptom variability in CFS are varied and include: ion channel dysfunction (Chaudhuri and Behan, 2000); the reactivation of viruses (Patarca-Montero, 2002); sleep deprivation, social disruption; reduced physical activity (Williams et al., 1996); as well as intermittent physical and/or emotional stress that may trigger an abnormal neuroendocrine function (Demitrack, 1994). Additionally, Tomoda et al. (2001) suggest that biological rhythm disturbances demonstrated in some CFS participants could be a consequence of changes in cerebral blood flow or metabolism.

Post-intervention results for all resting and physiological variables were similar to baseline scores in both groups, once again demonstrating minimal variation in these measures. However, post-intervention reliability scores for psychological variables showed that graded exercise resulted in reduced variability, and hence the reclassification of all psychological variables to a higher reliability category, except for physical fatigue scores which were less variable, but not enough to be reclassified. Reduced variability in psychological scores may be related to reported improvement in these symptoms after a graded exercise intervention (Fulcher and White, 1997; Powell et al., 2001; Wallman et al., 2004; Weardon et al., 1998). It is feasible to presume that if the sensation of a symptom is reduced, then this is likely to minimize the number of times that the sufferer notices it. Of interest, is that post-intervention reliability scores for anxiety also improved in the relaxation/stretching group. This is not surprising as relaxation and stretching techniques have been reported to reduce stress and consequently anxiety (Freidberg, 1995; Lewis et al., 1994), which may in turn reduce variability in this symptom over time.

Finally, improvement in reliability for post-intervention scores recorded on the Stroop Color Word test was noted in both groups. Graded exercise has been suggested by Blackwood et al. (1998) to improve automaticity in physical movement, which may result in the freeing up of attentional processes that can then be diverted to cognitive function. This could consequently minimise variation in cognitive processing. Improved reliability in cognitive scores after relaxation/stretching therapy could be due to the ability of this particular therapy to reduce stress, which may in turn improve cognitive function and subsequently reduce variability.

A paradox exists between the results shown in this study and the fluctuating nature of symptoms and physical capabilities commonly reported by CFS...
sufferers. An explanation could be that as mental and physical fatigue represent the defining symptoms of CFS, any variation felt by some sufferers in these symptoms may be transferred in a general sense to other symptoms. Additionally, variations in the sensation of fatigue may also contribute to global feelings of being well or unwell. Further to this, when CFS sufferers are specifically required to isolate and rate sensations, they may be able to then differentiate between any variances in these symptoms. Another explanation could be that symptoms and physical capabilities in CFS may fluctuate over a 24 hour period. If this is the case, then the protocol used in this study was not designed to monitor and record these changes. Further to this, questionnaires used to record feelings of anxiety, depression and fatigue required participants to report how they felt in the previous week, including the day of testing. While it is likely that responses would have mostly reflected subjective feelings on the day of testing, it would be better in future studies to require participants to record how they were feeling at the exact time of testing only.

Further research that involves regular repeated assessment of commonly reported symptoms in CFS over a period of time longer than four weeks, using different assessment instruments, could provide more insight into the complaint of high symptom variability in this disorder.

CONCLUSIONS

Questionable reliability scores recorded for mental and physical fatigue prior to the commencement of the interventions supports a variable nature to these symptoms in CFS. Conversely, scores for all other measures assessed were shown to vary minimally over a four-week period. Results from this study suggest that future studies, particularly those where participant numbers do not meet power requirements, should consider employing a repeated-measures analysis when assessing the symptoms of mental and physical fatigue in CFS participants and report the averaged results. Further to this, a twelve-week intervention of graded exercise was shown to reduce symptom variation in mental fatigue, as well as to improve the reliability of scores related to anxiety, depression, attention, and RPE at the end of the first minute of exercise.

REFERENCES


KEY POINTS

- Chronic fatigue syndrome sufferers often report a fluctuating nature to their symptoms and physical capabilities.
- Weekly assessment over a four-week period of psychological, physiological and cognitive variables demonstrated that only mental and physical fatigues were of questionable reliability.
- A 12-week graded exercise intervention resulted in the improvement of ICC scores for mental fatigue to that of acceptable reliability.
AUTHORS BIOGRAPHY

Karen E. WALLMAN
Employment
Lecturer, University of Western Australia
Degree
PhD
Research interests
Chronic fatigue syndrome, obesity.
E-mail: kwallman@cyllene.uwa.edu.au

Alan MORTON
Employment
Emeritus Professor, University of Western Australia
Degrees
PhD, Ed.D, FACSM
Research interests
Exercise induced asthma, chronic fatigue syndrome and cardio-respiratory response to acute and chronic exercise.
Email: amorton@cyllene.uwa.edu.au

Carmel GOODMAN
Employment
Lecturer, Sports Physician, University of Western Australia
Degree
MD
Research interests
Varied and includes chronic fatigue syndrome
Email: cgoodman@cyllene.uwa.edu.au

Robert GROVE
Employment
Professor, University of Western Australia
Degree
PhD
Research interests
Social psychology of exercise, health and sport.
Email: Bob.Grove@uwa.edu.au

Dr. Karen Wallman
School of Human Movement and Exercise Sciences, the University of Western Australia, Crawley, Western Australia