Randomised controlled trial of graded exercise in chronic fatigue syndrome

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ABSTRACT

Objective: To investigate whether 12 weeks of graded exercise with pacing would improve specific physiological, psychological and cognitive functions in people with chronic fatigue syndrome (CFS).

Design: Randomised controlled trial.

Setting: Human performance laboratory at the University of Western Australia.

Participants: 61 patients aged between 16 and 74 years diagnosed with CFS.

Interventions: Either graded exercise with pacing (32 patients) or relaxation/flexibility therapy (29 patients) performed twice a day over 12 weeks.

Main outcome measures: Changes in any of the physiological, psychological or cognitive variables assessed.

Results: Following the graded exercise intervention, scores were improved for resting systolic blood pressure ($P = 0.018$), work capacity ($W \cdot kg^{-1}$) ($P = 0.019$), net blood lactate production ($P = 0.036$), depression ($P = 0.027$) and performance on a modified Stroop Colour Word test ($P = 0.029$). Rating of perceived exertion scores, associated with an exercise test, was lower after graded exercise ($P = 0.013$). No such changes were observed in the relaxation/flexibility condition, which served as an attention-placebo control.

Conclusions: Graded exercise was associated with improvements in physical work capacity, as well as in specific psychological and cognitive variables. Improvements may be associated with the abandonment of avoidance behaviours.

MJA 2004; 180: 444–448

CHRONIC FATIGUE SYNDROME (CFS) is a common disorder that, despite intense research, still has an elusive aetiology, no conclusive laboratory marker, and no established cure. Graded exercise therapy and cognitive behavioural therapy are two management techniques that have consistently helped patients with CFS.[1] However, of the three randomised controlled trials that assessed graded exercise treatment,[2-4] none accounted for the cyclical nature of symptoms.[5,6] It is unclear whether the benefits reported reflected the outcome of the treatment, the fluctuating nature of the syndrome, or a combination of both. Additionally, two of the controlled trials used maximal oxygen consumption testing to assess physical function in CFS subjects.[2,4] This parameter is generally recognised as the gold standard for assessing cardiopulmonary function.[7] However, issues arise as to the suitability of using an exercise test that requires maximal effort from people with debilitating fatigue, particularly when this fatigue is exacerbated by physical activity.[8-10] Use of maximal oxygen consumption testing may deter some people with CFS from participating in trials and encourage the more robust or healthier subjects to volunteer for testing. This selection may influence the representativeness of the population with CFS in trials.

Our aims were:

- To confirm or refute the outcomes of previous trials that reported physiological and psychological improvements associated with graded exercise in CFS subjects.[2-4]
- To determine whether a 12-week program of graded exercise would result in a significant improvement in attentional function in CFS sufferers. To date, no study has assessed the effects of graded exercise on cognitive function in CFS.

METHODS

Recruitment

CFS subjects were recruited from notices placed in medical surgeries and by advertisements in local newspapers. Eighty-two patients (aged 16–74 years) applied to participate. Before participation, written confirmation of a CFS diagnosis, as defined by Fukuda et al,[11] was required from each subject's doctor. Fourteen applicants were excluded because of alternative diagnoses or failure to provide written confirmation of diagnosis. The remaining 68 patients were randomised (by an independent investigator) to a graded exercise or a relaxation/flexibility intervention. Six subjects withdrew from baseline testing for reasons not associated with the study, and a further subject was excluded because her body mass index ($44\ kg/m^2$) prevented her from participating in the exercise test. This left 32 CFS subjects in the graded exercise group (27 women, 5 men), and 29 CFS subjects in the relaxation/flexibility group (20 women, 9 men) (Box 1).

Based on an assumption of moderate effect size (0.4–0.6), a sample size of at least 30 subjects was needed in each intervention group to detect an effect at an α of 0.05 with 80% power.[12]

All subjects were assessed for depression as defined by the *Diagnostic and*

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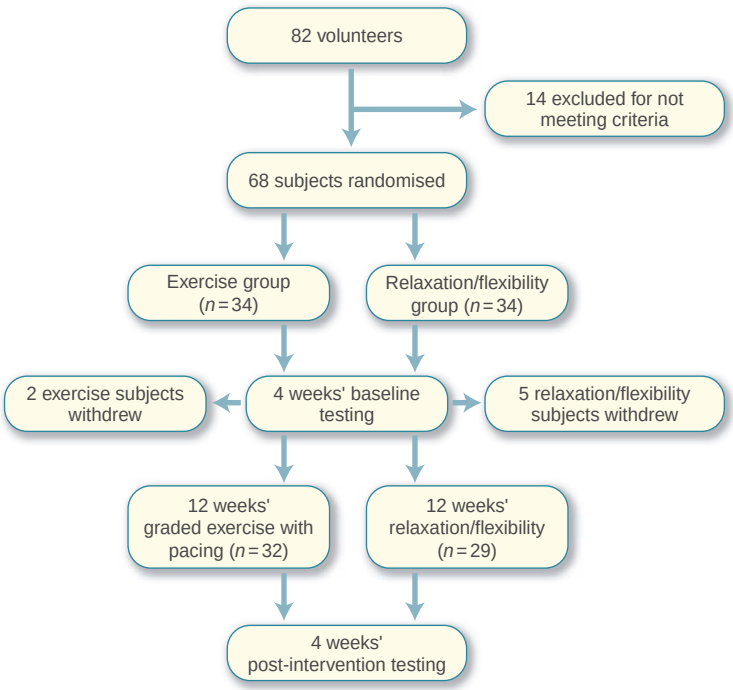
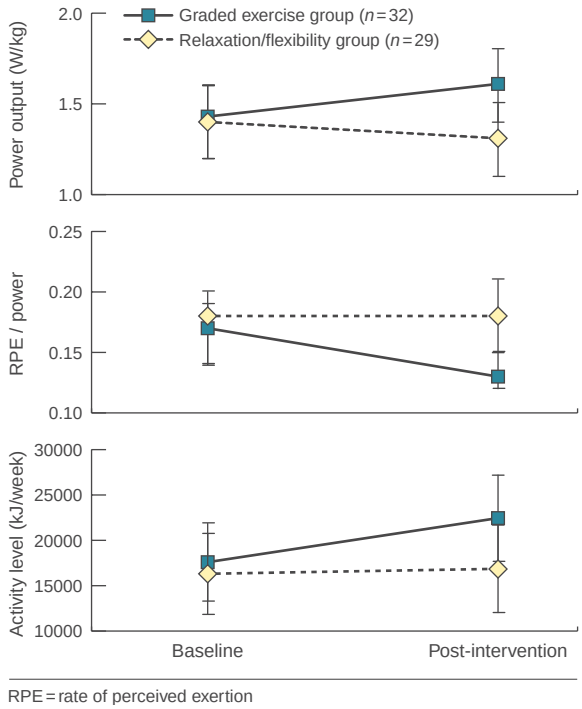
1: Overview of the study protocol



2: Changes (95% CIs) in selected physiological variables



RPE = rate of perceived exertion

statistical manual for mental disorders[13] using a computerised version of the Composite International Diagnostic Interview.[14]

Assessment

For the 4 weeks before and 4 weeks after the intervention, subjects attended weekly testing sessions at a university laboratory, on the same weekday at the same time. These assessment results were averaged for each 4-week period. The same exercise physiologist conducted all tests.

Resting heart rate (HR) and blood pressure (BP) were first recorded, then subjects were assessed on the Aerobic Power Index test,[15] a submaximal cycle test that has been shown to be reliable in a CFS population (intraclass correlation coefficient, 0.97).[16] This exercise test starts at low power and increases in small power increments until an individual target heart rate (THR: 220 – age 0.75) is reached.[15] The power output adjusted for body weight ($W \cdot kg^{-1}$) that coincided with a subject's THR was determined through interpolation techniques described by Telford and Minikin.[17] If a subject failed to reach the THR, the $W \cdot kg^{-1}$ achieved during the last full minute of exercise was recorded.

Ratings of perceived exertion (RPE), as measured by the Borg scale,[18] were recorded 55 seconds into each minute of the exercise test. Oxygen consumption was analysed continuously during the exercise test by a metabolic cart consisting of a computerised online system. Blood lactate was measured before and 3 minutes after the exercise test.

A similar interpolation procedure to that used to calculate power output at THR was used to determine RPE, oxygen uptake and respiratory exchange ratio values that coincided with each individual's THR. RPE values that equated to the subject's THR were divided by the final workload ($W \cdot kg^{-1}$) achieved either at or before THR. This ratio represents perceived exertion sensed at the end of the exercise test adjusted for the actual work done.

Weekly energy expenditure was determined using the Older Adult Exercise Status Inventory.[19] This scale excludes activities involving sitting or lying down.

Mental and physical fatigue was assessed using a 14-item self-rating scale,[20] and anxiety and depression were rated by the Hospital Anxiety and Depression Scale.[21]

Cognitive function was tested using a computerised version of the modified Stroop Colour Word test. This test has been used previously to assess attentional function in CFS.[22-24] We used two levels of difficulty based on speed of presentation.

On completion of the 12-week intervention, subjects indicated whether they felt the program had benefited them, using a global impression scale[25] from 1 ("Very much better") to 7 ("Very much worse").

Graded exercise program

Initial exercise duration was between 5 and 15 minutes, and intensity was based on the mean HR value achieved midpoint during the submaximal exercise tests. Graded exercise consisted of an aerobic activity that used the major large muscles of the body. Subjects could choose walking, cycling or swimming. Subjects were instructed to exercise every second day, unless they had a relapse. If this occurred, or if symptoms became worse, the next exercise session

was shortened or cancelled. Subsequent exercise sessions were reduced to a length that the subject felt was manageable. This form of exercise, which allows for flexibility in exercise routines, is known as pacing.[26]

Each subject was supplied with a small laminated Borg scale, and an HR monitor to help them reach and maintain their required HR goals. Subjects rated the effort of each exercise session and recorded their exercise details in a diary.

Subjects were contacted by phone every second week over the 12 weeks to review their progress and to determine their exercise regimen for the following fortnight.

Relaxation/flexibility program

The relaxation/flexibility group served as an attention-placebo control. Subjects were required to listen to a relaxation tape, and perform selected stretching exercises every second day for 12 weeks. All subjects kept a diary recording their relaxation/flexibility sessions.

Subjects were contacted by phone every second week to review their progress and to discuss the flexibility regimen for the following fortnight. Subjects participating in relaxation/flexibility were specifically requested not to participate in any extra physical activity while they were enrolled in the study.

The exercise physiologist attempted to spend the same amount of time on the phone with all subjects in both therapy groups.

Statistical analysis

Preliminary screening of the data indicated that all continuous variables were normally distributed. Analyses were conducted using 2 (group) 2 (time) mixed-model ANOVAs, with repeated measures on the time factor.[27] Significant interaction effects were examined further by post hoc comparison of group differences using F tests. Differences in ability to reach target HR during the exercise test were assessed using a Mann–Whitney non-parametric test. Results for the self-rated clinical global impression change score were collapsed in a 2 2 contingency table and compared using a χ^2 test corrected for continuity. All statistical procedures were performed using SPSS.[28]

3: Physiological scores (95% CIs)

	Graded exercise group (*n*=32)		Relaxation/flexibility group (*n*=29)		
	Baseline	Post-Intervention	Baseline	Post-Intervention	*P**
Resting values					
Resting heart rate (bpm)	75 (71–78)	72 (69–75)	74 (70–78)	74 (70–78)	0.038
Resting systolic BP (mmHg)	117 (112–121)	112 (108–116)	119 (114–124)	120 (115–125)	0.014
Resting diastolic BP (mmHg)	79 (76–82)	74 (71–76)	80 (76–84)	76 (74–79)	0.262
Exercise test values†					
Oxygen uptake ($mL \cdot kg^{-1} \cdot min^{-1}$)	15.6 (13.3–17.7)	17.1 (14.9–19.2)	15.8 (13.7–17.9)	14.4 (12.4–16.4)	0.001
Respiratory exchange ratio	0.97 (0.93–1.01)	1.03 (0.99–1.06)	0.98 (0.94–1.02)	1.00 (0.96–1.04)	0.047
Net blood lactate production (mmol/L)	1.7 (1.4–1.9)	1.8 (1.5–2.1)	1.6 (1.4–1.9)	1.4 (1.1–1.7)	0.025

bpm = beats per minute. BP = blood pressure. * *P* value for group time interaction. † Exercise test values are means of mean values at target heart rate (THR) for subjects who reached THR, and peak values for subjects who did not reach THR.

Ethics approval

This project was approved by the University of Western Australia Human Research Ethics Committee.

RESULTS

There were no initial differences between the treatment and control groups in age, body mass, height, activity levels or illness duration.

Six subjects were classified as having had a major depressive disorder in the previous 12 months (single episodes that ranged from mild to severe without psychotic features). Two other subjects were classified with dysthymia. Results presented include data from all subjects, because analyses that excluded data from the six subjects diagnosed with a previous major depressive disorder produced similar results.

Physiological results

Physiological results are shown in Box 2 and Box 3. Repeated-measures ANOVAs showed significant treatment by time interactions for all variables except resting diastolic BP.

We observed a significant improvement in resting systolic BP ($P=0.018$) and in $W \cdot kg^{-1}$ ($P=0.019$) in the exercise group. Improvement in $W \cdot kg^{-1}$ was reflected by a significant increase in net lactate production ($P=0.036$), as well as by the number of exercise tests on which THR was achieved by the exercise group during post-intervention testing ($P=0.030$) (Box 4). Oxygen uptake values were 9.6% higher after the intervention in the exercise group compared with an 8.9% decline in the relaxation/flexibility group, but the difference in final values for the groups was not significant. Of interest, ratings of perceived exertion were lower after the exercise intervention ($P=0.013$). Activity levels increased in the graded exercise group, although the final levels did not differ between the groups (Box 2).

Psychological results

Mean psychological scores are shown in Box 5. Post-hoc analysis showed that, while baseline depression scores were similar in both groups, scores were significantly lower in the exercise group following the intervention ($P=0.027$). While there were no other significant post-intervention differences, follow-up tests showed a significant improvement in mental fatigue over time in the exercise group ($P<0.001$).

4: Achievement of target heart rate (THR) during the exercise test

	Number (%) of tests in which THR was reached
Graded exercise group (*n*=128)	
Baseline	89 (70%)
Post-intervention	95 (74%)
Relaxation/flexibility group (*n*=116)	
Baseline	74 (64%)
Post-intervention	61 (53%)

5: Psychological, cognitive and general health scores

	Graded exercise (*n*=32)		Relaxation/flexibility (*n*=29)		
	Baseline	Post-intervention	Baseline	Post-intervention	*P*
Psychological results					
HADS:* depression	6.5 (5.3–7.6)	4.8 (3.6–5.9)	7.1 (5.9–8.2)	6.5 (5.5–7.6)	0.041
HADS:* anxiety	7.3 (5.8–8.7)	5.7 (4.4–6.9)	8.7 (7.5–9.9)	7.8 (6.5–9.2)	0.242
Mental fatigue†	6.3 (5.6–7.0)	4.5 (3.9–5.2)	5.6 (5.0–6.1)	4.8 (4.2–5.5)	0.023
Physical fatigue†	11.6 (10.1–13.0)	8.1 (6.9–9.4)	11.4 (10.4–12.3)	9.6 (8.3–10.9)	0.074
Cognitive results					
Stroop test (82 questions)	73.7 (68.0–79.3)	79.4 (78.0–80.8)	70.0 (61.3–78.9)	71.1 (63.3–78.9)	0.147
Stroop test (95 questions)	80.1 (73.1–87.0)	87.5 (81.4–93.6)	75.8 (64.6–87.0)	73.1 (60.3–85.9)	0.014

* HADS = Hospital Anxiety and Depression Scale,[21] a 14-point scale on which a score < 8 is considered non-pathological. † Maximum possible scores for mental and physical fatigue are 12 and 21, respectively. A combined fatigue score of ⩾ 8 and existence of fatigue for at least 6 months is used to define a condition of chronic fatigue.

On the modified Stroop Colour Word test, there were no significant differences between the groups before the intervention, but a significant difference in favour of the graded exercise group after the intervention on the more difficult level of this test ($P = 0.029$) (Box 5).

Self-rated impression of benefit

Box 6 shows the scores on the self-rated clinical global impression change scale. Although there was no significant difference between the two groups ($\chi^2 = 1.46$; df = 1; $P = 0.227$), a greater percentage of subjects in the exercise group rated themselves as being better (exercise group, 29/32 [91%]; relaxation group, 22/29 [76%]).

DISCUSSION

Our physiological results support those reported by others,[2,4] in that a graded exercise program resulted in a significant improvement in work capacity ($W \cdot kg^{-1}$). The ability to do more work after graded exercise was also reflected by significantly higher net lactate production and by a significant improvement (6.7%) in the ability of subjects in this group to reach their THR. This improved ability to do more work may be because the exercise regimen was not associated with any relapse. This may have resulted in the abandonment of the commonly held belief by CFS sufferers that exercise results in the exacerbation of symptoms, which consequently leads to the avoidance of exercise.[29,30] Additionally, graded exercise was associated with a reduction in perceived effort scores associated with the exercise test. Many studies have documented that CFS subjects report a greater sense of effort associated with exercise tests compared with control subjects.[9,31,32] Gibson et al[9] suggest that an abnormal sense of effort in CFS may be the result of the resetting of a sensory threshold in response to the initial onset of symptoms, and that this then becomes a learned response. Results from our study suggest that 12 weeks of graded exercise intervention may have resulted in a further resetting of this sensory threshold toward more normal values. Of importance is the implication that this reduced sense of effort may be associated with everyday work tasks that require similar work capacities.

Scores for depression improved after graded exercise, and mental fatigue decreased. Reduced symptoms of fatigue after graded exercise intervention have been previously reported.[2,4] These psychological improvements may be due to improved physical capacity and the potential of aerobic exercise to increase core body temperature, which can reduce muscle tension and stress[33] and consequently improve sleep patterns.[34] Reduced psychological symptoms may also result in attenuated afferent feedback to the motor cortex in CFS subjects, which can subsequently reduce effort sensation.[35]

Our graded exercise intervention was also associated with an improvement in attentional function. To date, little has been reported about the effects of aerobic exercise on cognitive performance. Christodoulou et al[36] reported an association between inactivity and increased errors made on neuropsychological tests by CFS subjects, and Vercoulen et al[37] reported a relationship between low levels of activity and impaired cognitive function in CFS subjects, demonstrated by slowed speed of information processing. It has been proposed that lack of physical and cognitive practice reduces automatic function in these areas in CFS sufferers, which makes physical and cognitive tasks more effortful.[31,38] Furthermore, it has been postulated

6: Self-rated clinical global impression change scores after completing treatment

Rating	Graded exercise* (*n*=32)	Relaxation/flexibility* (*n*=29)
1: Very much better	5 (16%)	2 (7%)
2: Much better	14 (44%)	10 (34%)
3: A little better	10 (31%)	10 (34%)
4: No change	3 (9%)	6 (21%)
5: A little worse	0	1 (3%)
6: Much worse	0	0
7: Very much worse	0	0

* Values are number (%) of people choosing each rating.

that a graded return to cognitive and physical activities may assist CFS sufferers in regaining automaticity in these functions, as well as reduce the sense of effort associated with these tasks.[31]

Most subjects (91%) rated themselves as feeling better after the exercise intervention, and no subject felt that graded exercise worsened their symptoms.

Limitations of the study relate to the use of a relaxation/flexibility control group rather than a control group that experienced no intervention, and neither subjects nor the exercise physiologist were blinded to the intervention. Additionally, 12 weeks may not have been long enough to maximise changes. Further studies that include a longer intervention period and a formal follow-up would provide valuable information in this debilitating disorder.

CONCLUSION

Our study showed that a graded exercise intervention that included a form of pacing was associated with specific physiological, psychological and cognitive improvements as compared with a control regimen of relaxation/flexibility. An important aspect of our study was that graded exercise was not associated with a relapse in any participant. While not a cure for CFS, graded exercise improves functional ability, and minimises deconditioning, which can result in more symptoms.

COMPETING INTERESTS

None identified.

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(Received 16 Sep 2003, accepted 8 Dec 2003) ❑