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Nijs, J. and Almond, F. and De Becker, P. and Truijen, S. and Paul, L.
(2008) Can exercise limits prevent post-exertional malaise in chronic
fatigue syndrome? An uncontrolled clinical trial. *Clinical Rehabilitation*
22(5):pp. 426-435.

<http://eprints.gla.ac.uk/4155/>

1st June 2009

Can exercise limits prevent post-exertional malaise in chronic fatigue syndrome? An uncontrolled clinical trial.

Jo Nijs ^{1,2}, PhD, MSc, PT; Freya Almond ¹, PT; Pascale De Becker ¹, PhD, PT; Steven Truijen ², PhD; Lorna Paul ³, PhD, PT

¹ Department of Human Physiology, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Belgium

² Division of Musculoskeletal Physiotherapy, Department of Health Care Sciences, University College Antwerp, Belgium

³ Division of Nursing and Health Care, Faculty of Medicine, University of Glasgow, Glasgow, United Kingdom

Address of correspondence and reprints requests to Dr Jo Nijs (assistant professor), University College Antwerp, Van Aertselaerstraat 31, B-2170 Merksem, Belgium (phone +32 3 6418265 fax +32 3 641827 e-mail j.nijs@ha.be).

Key words: exercise, chronic fatigue, syndrome, fibromyalgia, pain, therapy

ABSTRACT

Objective: It was hypothesized that the use of exercise limits prevents symptom increases and worsening of their health status following a walking exercise in people with Chronic Fatigue Syndrome (CFS).

Design: An uncontrolled clinical trial (semi-experimental design).

Setting: Outpatient clinic of a university department.

Subjects: 24 patients with CFS.

Interventions: Subjects undertook a walking test with the two concurrent exercise limits. Each subject walked at an *intensity* where the maximum heart rate was determined by heart rate corresponding to the respiratory exchange ratio =1.0 derived from a previous sub-maximal exercise test and for a *duration* calculated from how long each patient felt they were able to walk.

Main outcome measures: The Short Form 36 Health Survey or SF-36, the CFS Symptom List, and the CFS-Activities and Participation Questionnaire were filled in prior to, immediately and 24 hours post-exercise.

Results: The fatigue increase observed immediately post-exercise ($p=0.006$) returned to pre-exercise levels 24 hours post-exercise. The increase in pain observed immediately post-exercise was retained at 24 hours post-exercise ($p=0.03$). Fourteen of 24 subjects experienced a clinically meaningful change in bodily pain (change of SF-36 bodily pain score ≥ 10). Six of 24 participants indicated that the exercise bout had slightly worsened their health status, and 2 of 24 had a clinically meaningful decrease in vitality (change of SF-36 vitality score ≥ 20). There was no change in activity limitations/participation restrictions.

Conclusion: It was shown that the use of exercise limits (limiting both the intensity and duration of exercise) prevents important health status changes following a walking exercise in people with CFS, but was unable to prevent short-term symptom increases.

Introduction

There is evidence to support specific exercise therapies as a cornerstone in the comprehensive management of Chronic Fatigue Syndrome (CFS).¹⁻³ The evidence from individual randomised clinical trials is underscored by the conclusions of a systematic literature review by the Cochrane Collaboration.⁴ However, too vigorous exercise⁵⁻⁷ or a 30% increase in activity⁸ frequently triggers post-exertional malaise in people with CFS, a primary characteristic evident in up to 95% of people with CFS.⁹ The severe exacerbation of symptoms following exercise, as seen in CFS patients, is not present in other disorders where fatigue is a predominant symptom such as depression, rheumatoid arthritis, systemic lupus erythematosus, or multiple sclerosis.^{10,11} Indeed a recent study has shown that post-exertional malaise was one of the best predictors of the differential diagnosis of CFS and major depressive disorder.¹² Success of exercise therapy in CFS most likely relates initially to its ability to demonstrate to sufferers that exercise can be safely undertaken without the consequence of post-exertional malaise, therefore assisting CFS sufferers to abandon any avoidance behaviors to which they may have previously adhered.¹³ Thus, exercise-induced symptom exacerbations must be prevented.

In order to prevent exercise-induced symptom exacerbations, it seems plausible to use individually tailored exercise limits. There is limited evidence available supporting this notion: patients with CFS are generally able to perform light to moderate exercise (40% of peak oxygen capacity) without exacerbating their symptoms or cognitive performance.^{14,15} Still, more work in this area is required to enable clinicians to prevent post-exertional malaise when applying exercise therapy to people with CFS. The present study examined the effect of applying two methods of individually tailored exercise limits in preventing symptom increases and worsening of their health status following an exercise bout.

The first exercise limit was related to the *duration* of exercise and was determined by the patient's report of how long they were able to walk without increasing their symptoms. It has been suggested that people with CFS need to learn to estimate their current physical capabilities prior to commencing an exercise,¹⁶ keeping in mind the regular fluctuating nature of their symptoms.^{17,18} In the absence of irrational fear of movement, the patient's estimated exercise duration can be reduced to account for typical overestimations made by the patient. The second exercise limit was related to the *intensity* of the exercise. The intensity of exercise was again calculated on an individual basis based on the results of a sub-maximal exercise test. The respiratory quotient reflects the quantity of carbon dioxide produced in relation to oxygen consumed. Under conditions other than steady-rate exercise, various factors can alter the exchange of oxygen and carbon dioxide in the lungs so that the respiratory quotient no longer reflects the substrate mixture in energy metabolism; the quotient is now termed the respiratory exchange ratio (RER).¹⁹ Exhaustive exercise presents such a condition where RER can rise significantly above 1.0 due to buffering of lactic acid generation during anaerobic metabolism.¹⁹ Heart rate recommendations derived from incremental exercise stress tests are frequently used for monitoring exercise intensity in healthy people²⁰ and patients with CFS.^{1,2} During the walking test in the present study, the maximum heart rate was taken to be the heart rate corresponding to RER=1.0 derived from a submaximal incremental exercise test.

It was hypothesized that by walking for a period of time determined from the subject's estimation of their exercise ability (*duration*) whilst at the same time maintaining a heart rate lower than the heart rate corresponding to RER=1.0 (*intensity*), prevents symptom increases following a walking exercise in people with CFS. Likewise, it was hypothesised that our approach to limiting exercise intensity and duration would prevent worsening of their health status up to 24 hours post-exercise.

Methods

Design

A repeated measures semi-experimental design was used to examine the hypotheses. The local ethics committee (University Hospital Brussels; O.G. 016) approved the study protocol. During the first testing day, patients providing informed consent were asked to perform a submaximal graded bicycle ergometric test to assess the heart rate and oxygen uptake corresponding to RER=1.0, and thus to establish the maximum heart rate which would be used to limit the intensity of exercise during the walking test (as below).

The patient returned to the university at least 2 and maximally 4 weeks later, to undertake the walking exercise (figure 1 displays the flow diagram of the study). On the second testing day, study participants were asked to fill in three self-reported measures, and then undertook the walking exercise with continuous heart rate monitoring. After termination of the walking exercise, the patients were given the opportunity to drink mineral water ad libidum, and were asked to fill in the same self-reported measures. Afterwards, the subjects were given a sealed envelope containing the self-reported measures and a stamped, addressed return envelope.

The subjects were instructed to fill in the questionnaires once more exactly 24 hours later and to return them to our university. Approximately 24 hours after terminating the walking exercise, subjects were contacted by telephone to ask whether their condition had improved, worsened or unchanged within the past 24 hours. In addition, they were asked whether or not they had taken additional medication to reduce symptoms, and were prompted to complete the questionnaires if they had not already done so.

Subjects

Patients with CFS were allocated from consecutive referrals to a specialised chronic fatigue clinic (sample of convenience). All participants fulfilled the Centre for Disease Control and Prevention criteria for CFS.¹⁷ All patients underwent an extensive medical evaluation prior to study participation (for more details regarding the diagnostic strategies as applied in this study, see reference 21). Additional inclusion/exclusion criteria beyond the diagnostic criteria were applied: all participants had Dutch as their native language, were within the age range of 18 to 65 years, had to be able to walk and to perform a submaximal bicycle exercise test, and had to be willing to visit the university twice for study participation. Finally, all participants had to provide written informed consent.

Submaximal exercise stress test

Before each test, gas and volume calibration took place with a 3-l syringe, according to the manufacturer's guidelines. The oxygen analyzer was calibrated with known gas mixtures of 18% O₂ and 5% CO₂. The room air calibration was automatically run before each test to update the CO₂ analyzer baseline and the O₂ analyzer gain so that they coincided with atmospheric values. The patients performed a bicycle ergometric test using a linear increase in workload. The patients sat on an electromagnetically braked ergometer (Jaeger 900; Lode B.V., Groningen, the Netherlands). Heart rate was monitored continuously during exercise using a Polar Accurex PlusTM (Polar Electro OY, Kempele, Finland). In order to collect pulmonary data during the test, an open circuit spirometer (Mijnhart Oxycon; IBM, Bunnik, the Netherlands) with automatic printout every 30 seconds was used. Averages were obtained for oxygen uptake and carbon dioxide production during every 30-second interval for the duration of each stage of the exercise. A 2-way breathing valve attached to a mask, which covered the patients' nose and mouth, was used to collect the expired air. The air was

analyzed continuously for ventilatory and metabolic variables. Patients started the test at 10W, with a linear increase of 10W/minute. Patients were instructed to cycle at a constant speed of 60 revolutions/minute. In order to ascertain the valid collection of the physiological exercise data at RER=1.0, the test was continued until RER approached 1.1. The following variables were measured: heart rate at RER=1.0 (HR_{RER1}), exercise duration, oxygen uptake at RER=1.0 (VO_{2RER1}) per kilogram of body weight, and body weight-adjusted oxygen uptake at RER=1.0.

Walking exercise and exercise limits

Walking was chosen because it is a mode of exercise which is very functionally relevant, easily applied in the clinical setting and frequently used in exercise therapy for people with CFS.^{1,2} Prior to the walking exercise, the patients were asked to indicate how long they would be able to walk on a flat surface without increasing symptoms, and whether they were currently experiencing a good or a bad day. In order to account for typical overestimations, the patient's estimated exercise duration was reduced with 25 of 50 % in case of a good or a bad day respectively. This was used to limit the walking *duration*. In addition, the exercise *intensity* was limited using an upper heart rate limit corresponding to the RER=1.0 (derived from the submaximal exercise stress test). Heart rate was monitored continuously during exercise using a Polar Accurex PlusTM (Polar Electro OY, Kempele, Finland). The heart rate corresponding to RER=1.0 was entered in the heart rate monitor as the upper limit. The patients were asked to walk on a flat surface and in a straight line from one marking spot to another (the 2 marking spots were placed at a 10 m distance). The patient was instructed to walk at a steady pace, not to talk or to stop walking during the exercise, and to decrease the walking pace if the alarm went of (i.e. when the heart rate increased above the

upper limit). The investigator recorded the walking distance and the number of times the alarm sounded.

Outcome measures

The Medical Outcomes Short Form 36 Health Status Survey or SF-36 assesses functional status and well-being or quality of life.²² The SF-36 has been documented to have reliability and validity in a wide variety of patient populations²²⁻²⁴ and it appears to be the most frequently used measure in CFS research.²⁵

The CFS Symptom List is a self-reported measure for assessing symptom severity in CFS patients. It encompasses the 19 most frequently reported symptoms in a sample of 1578 CFS patients.²⁶ In order to assess the severity of the symptoms included in the CFS Symptom List, visual analogue scales (100 mm) are used. In a previous study in 68 CFS patients, the internal consistency of the different items included in the Dutch CFS Symptom List was high (Cronbach's $\alpha = 0.88$).²⁷ The CFS Symptom List displayed excellent test-retest reliability (ICC ≥ 0.97), content and concurrent validity (manuscript in review).

The CFS-Activities and Participation Questionnaire or CFS-APQ is a self-administered questionnaire aimed at monitoring activity limitations and participation restrictions in patients with CFS. A total score of 1 indicates no activity limitations or participation restrictions while 16 represents the maximum score. Data documenting the test-retest reliability, internal consistency, content, convergent, and discriminant validity of the Dutch CFS-APQ in CFS patients have been reported.^{28,29}

Data analysis

All data were analysed using SPSS 14.0[®] for Windows (SPSS Inc. Headquarters, 233s. Wacker Drive, 11th floor, Chicago, Illinois 60606, USA). The sample size was

determined on the basis of the post-hoc power analysis performed after analysing the data of the first 11 subjects completing the study. The data of the 11 subjects were analysed for potential pre- versus post-exercise differences using a Friedman 2-way analysis of variances and subsequent post-hoc power analysis, revealing that at least 22 subjects were required to obtain a Power ($1-\beta$) of 0.80. For analysing the data of the entire study sample ($n=24$), a one-sample Kolmogorov-Smirnov goodness-of-fit test was used to examine whether the variables were normally distributed. In case of normality, potential differences between the first, second, and third assessment were examined using repeated measures analysis of variances and post-hoc paired samples t-testing. Variables that were not normally distributed were analysed using the non-parametric Friedman 2-way analysis of variances for 3 related samples. In order to account for missing data, the 'last observation carried forward method' was used for intention-to-treat analysis. The level of significance was set at 0.05. Effect sizes of the SF-36 subscale scores were counted and interpret according to method described in reference 30.

Results

The mean age of the study participants (n=24) was 37.6 ± 9.3 years (range [20-56]), their weight ranged between 45 and 101 kilograms (mean= 65.6 ± 14.8), their height between 153 and 179 centimetres (mean= 168.8 ± 7.4), and the majority were female (20 of 24 participants or 83.3 %).

The physiological data obtained during the submaximal exercise stress test are presented in table 1. Of particular interest is the heart rate corresponding to RER=1.0, which was used to limit the walking exercise during the second testing day. On the day of the walking exercise, only 9 of 24 participants (37%) were experiencing a good day. During the exercise bout, the heart rate of the majority of participants (19/24 or 79%) remained below their heart rate limit (i.e. the heart rate corresponding to RER=1.0). In five cases, the heart rate alarm went off at least once (range [1-16]) during the exercise bout, forcing them to decrease their walking speed. The performance data of the walking exercise are presented in table 2.

The comparison of the pre- versus post-exercise symptom severity and health status scores are presented in Table 3. One participant failed to return the 24 hours post-exercise questionnaires, leaving us with only pre-exercise and immediately post-exercise questionnaires for that participant. The 'last observation carried forward method' was used as intention-to-treat analysis, but this did not alter the results presented below (data not shown). There was no change in self-reported activity limitations / participation restrictions or total scores on the CFS Symptom List between the 3 assessments (pre-exercise, immediately and 24 hours post-exercise). However, fatigue and musculoskeletal pain worsened in response to the walking exercise. The fatigue increase observed immediately post-exercise ($t=-3.0$; $p=0.006$) improved in the next 24 hours and no longer differed from the pre-exercise scores at 24 hours post-exercise ($t=-1.9$; $p=0.07$). The increase in musculoskeletal pain observed immediately post-exercise ($t=-3.7$; $p=0.001$) was retained at 24 hours post-exercise ($t=-2.3$;

p=0.03). Likewise, the bodily pain subscale score of the SF-36 worsened from pre- to post-exercise ($t=2.5$; $p=0.02$), and this situation remained at 24 hours post-exercise ($t=2.9$; $p=0.009$). Effect sizes of the SF-36 subscale scores were counted and interpreted according to method described in reference 30. Fourteen of 24 subjects experienced a clinically meaningful change in bodily pain (i.e. a minimum change of the SF-36 bodily pain subscale score of 10). Apart from the symptom 'sore throat', no other symptoms included in the CFS Symptom List changed in response to the walking exercise (data not shown). The severity in sore throat increased from pre- to 24 hours post-exercise ($t=-3.5$; $p=0.002$), but this change was largely due to the increase from immediately post-exercise to 24 hours post-exercise ($t=-2.7$; $p=0.01$), and not due to a change from pre- to immediately post-exercise ($t=-1.8$; $p=0.09$).

At 24 hours post-exercise, the majority of participants (18/24 or 75%) reported that their health status had not changed within the past 24 hours, and the remaining participants (6/24) indicated that the exercise bout had slightly worsened their health status. None of the participants had taken additional medication to relief the worsening of their health status. Analysing the mean SF-36 subscale scores over time, general health perception, physical functioning, social functioning, mental health, role limitations due to emotional problems or due to physical functioning did not change in response to the walking exercise. Although a decrease in vitality was observed both immediately ($t=2.2$; $p=0.04$) and 24 hours post-exercise ($t=2.8$; $p=0.01$), 2 of the 24 patients had a clinically meaningful change in vitality (i.e. a minimum change of the SF-36 vitality subscale score of 20³⁰).

Discussion

It was shown that the use of exercise limits (limiting both the intensity and duration of exercise) prevents important health status changes following a walking exercise in people with CFS, but was unable to prevent short-term symptom increases. Although the mean total score on the CFS Symptom List did not change in response to the exercise bout, an acute increase in fatigue and musculoskeletal pain was observed. Fatigue severity returned to its pre-exercise level at 24 hours post-exercise, but the worsening of musculoskeletal pain was still evident at 24 hours post-exercise. The majority of subjects (58%) experienced a clinically meaningful increase in bodily pain. In addition, sore throat severity was increased at 24 hours post-exercise. Experiencing a sore throat in response to exercise has previously been reported in people with CFS.^{6,14} Thus, it seems the walking exercise triggered a short-term increase in fatigue and worsening of musculoskeletal pain for at least 24 hours post-exercise. Still, given the short-term effects on fatigue and the limited (approximately 10% on a visual analogue scale) increase in musculoskeletal pain, the exercise bout did not trigger severe post-exertional malaise but a limited symptom increase. This conclusion is further supported by the fact that no participant needed to use medication post-exercise to account for their symptom increase. The short-term effects on fatigue as observed here, together with the previous report of fatigue increase up to 12 days (mean 8.8 days) after a maximal exercise bout,⁶ suggests that exercise limits can limit post-exertional increase in fatigue. In summary, the use of the heart rate corresponding to RER=1.0, together with the self-paced exercise duration did completely prevent symptom increases following a walking exercise, but did not trigger severe malaise either.

In addition, it was hypothesised that our approach to limiting exercise intensity and duration would prevent worsening of the patients' health status post-exercise. Our data are partly in support of this hypothesis: the walking exercise did not alter activity limitations /

participation restrictions, general health perception, physical functioning, role limitations due to emotional problems, mental health, social functioning, or role limitations due to physical functioning. On the other hand, 25% of the participants reported at 24 hours post-exercise that the exercise bout had slightly worsened their health status, and a slight decrease in vitality was observed up to 24 hours post-exercise. Only a small proportion of the patients (8%) had a clinically meaningful decrease in vitality, questioning the clinical importance of the observed statistically significant change in vitality. It is concluded that the present approach of limiting exercise intensity does not completely prevent worsening of health status in all people with CFS, but it does not trigger important changes in health status either. These data in relation to both symptom and health status changes in response to a paced walking exercise highlight the fact that physiotherapists and rehabilitation specialists should be cautious when using exercise in people with CFS. However the results for a minority of the subjects studied here support the notion that the exercise intensity necessary to cause a symptom increase can be quite mild.³¹ The present approach to exercise may be useful in preventing important changes in health status of people with CFS, but further studying of the ability of other exercise limits to prevent worsening of symptoms and health status in response to exercise in people with CFS is warranted. In this regard, it might be useful to consider that 63% of our subjects were only walking for 50% of the time they estimated they could walk, supporting the anecdotal evidence of typical overestimations in people with CFS.

Our results are consistent with those reported by Clapp et al¹⁴ who studied the acute effects of 10 discontinuous, 3 minutes exercise bouts on a treadmill in 10 patients with CFS. There was a 3-minute recovery period between exercise bouts, and the participants walked at a comfortable walking pace self-selected by the subjects, as was the case in our study. On average, their subjects walked at a speed of 0.71 ± 0.20 m/s, which is slightly lower as compared to our subjects (0.9 ± 0.2 m/s). The results were in line with our findings: it was

found that the symptoms did not worsen severely after exercise, but some patients reported experiencing headaches, leg pain, fatigue, or sore throats. As was the case in our study, there was no change in the degree of disability or general health status. Others used a maximal bicycle exercise stress test to determine the submaximal exercise intensity (40% of peak oxygen uptake) for a 25 minutes exercise bout approximately 2 weeks later.¹⁵ Analysing the group data, the exercise bout had no effect on tiredness, energy, or cognitive performance. In our study, submaximal exercise testing was chosen to determine exercise intensity because it is unlikely in itself to cause significant increase in symptoms as may occur following peak exercise testing,³² making it difficult to compare our results to the ones reported by Cook et al¹⁵. Still, the use of the heart rate corresponding to RER=1.0 was chosen as a non-invasive, indirect way of achieving aerobic exercise. It has previously been shown that 15 minutes of sub-anaerobic (at 90 % of their predicted work rate at their anaerobic threshold) bicycle exercise did not exacerbate gait parameters in people with CFS.³³ Since direct monitoring of the physiological exercise response during the walking test was not performed, we are unable to state that the walking exercise was performed at an aerobic level. The use of the heart rate corresponding to RER=1.0 as an exercise limit is likely to prevent anaerobic exercise, even in people with CFS.

Addressing the study limitations, the lack of additional physiological monitoring during the walking exercise has been mentioned. On the other hand, use of physiological measurements during exercise is unlikely to reflect a clinical approach to exercise in people with CFS. In addition, the concept of post-exertional malaise requires an objective definition with one or more cut-off criteria. In this view, a control group not performing any exercise throughout the trial would have strengthened the study, especially given the fluctuating nature of the illness. On the other hand, since even routine daily activities like ironing frequently trigger symptom increases, it would be extremely difficult to ascertain no ‘damaging’ physical

activity in the untreated control group. The latter issue applies to the 24 hours post-exercise assessment of the present study as well: the observed changes at 24 hours post-exercise might not be related to the walking exercise, but instead triggered by other physical demanding activities. The symptom and health status changes observed immediately post-exercise are unlikely to be biased: the study participants had no opportunity to do anything else besides the walking exercise between the first and the second assessment. Another study limitation addresses the external validity of the results: as is the case in many, if not all studies on exercise in CFS, the results can only be extrapolated to those having at least some training load. Finally, it is unclear whether the level of exercise which was undertaken would be sufficient to improve cardiovascular fitness and reduce deconditioning. More work is required to address the issue of prevention of post-exertional malaise in people with CFS, for instance by using exercise limits as previously used in randomised controlled clinical trials of exercise therapy in people with CFS (e.g. exercise intensity based on the heart rate value obtained midpoint during a submaximal exercise test ² or the heart rate corresponding to 40% of peak oxygen consumption during a maximal exercise test ¹).

In conclusion, it was shown that the use of the heart rate corresponding to RER=1.0, together with the self-paced exercise duration, resulted in a short-term worsening of fatigue and an increase in pain up to 24 hours post-exercise. The concomitant use of 2 exercise limits did prevent health status changes following a walking exercise in people with CFS. Thus, the present data suggest that exercise limits can prevent post-exertional malaise, but cannot prevent an acute symptom increase post-exercise in people with CFS. Future studies could address the study limitations of the present study to examine the ability of other exercise limits to prevent worsening of symptoms and health status in response to exercise in people with CFS.

Clinical messages

- The use of the heart rate corresponding to RER=1.0 as an exercise limit, together with the self-paced exercise duration did not trigger severe post-exertional malaise but a limited symptom increase in fatigue, pain and sore throat severity.
- The concomitant use of 2 exercise limits prevents health status changes following a walking exercise in people with CFS.

Acknowledgements

The authors are grateful to Lieve De Hauwere for aiding in the data collection, and to Kenny De Meirleir for diagnosing the study participants.

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Table 1. Physiological data of the submaximal exercise stress test (n=24).

Submaximal exercise parameter	Mean \pm SD*	Range
Exercise duration at RER [†] =1.0 (minutes)	6.2 \pm 2.5	[1.5-11.5]
Heart rate at RER=1.0 (bpm)	119.2 \pm 14.3	[94-146]
VO ₂ [‡] at RER=1.0 (l/min)	853.8 \pm 294.8	[363-1372]
VO ₂ /body weight at RER=1.0 (ml/kg per min)	13.3 \pm 4.0	[6.4-20.6]

*SD=standard deviation; [†]RER=respiratory exchange ratio; [‡]VO₂ = oxygen uptake

Table 2. Performance data of the walking exercise (n=24).

Walking exercise parameter	Mean \pm SD*	Range
Exercise duration (minutes)	18.2 \pm 11.7	[5-60]
Walking distance (m)	558 \pm 340	[120-1620]
Speed (m/s)	0.9 \pm 0.2	[0.6-1.1]
Heart rate at termination of exercise (bpm)	92.6 \pm 15.6	[66-132]

*SD=standard deviation

Table 3. Comparison of pre- versus post-exercise symptom and health status scores.

	Pre-exercise (mean ± standard deviation)	Immediately post- exercise (mean ± standard deviation)	24 hours post- exercise (mean ± standard deviation)	ANOVA (F; p)
n	24	24	23	
CFS-APQ	6.9 ± 1.9	7.0 ± 1.7	7.0 ± 1.9	1.4 ; 0.3
CFS Symptom List total score	39.9 ± 14.7	41.6 ± 15.4	40.5 ± 17.9	0.4 ; 0.6
VAS fatigue	48.9 ± 23.1	62.1 ± 24.3	58.0 ± 28.8	4.1 ; 0.02
VAS musculoskeletal pain	32.8 ± 24.5	44.0 ± 29.9	41.7 ± 31.0	5.9 ; 0.01
VAS sore throat	13.2 ± 17.9	16.4 ± 23.5	26.7 ± 26.9	9.2 ; 0.002
SF-36 bodily pain	60.4 ± 22.0	55.6 ± 22.2	55.3 ± 20.3	5.0 ; 0.01
SF-36 physical functioning	52.5 ± 21.2	49.8 ± 19.6	50.7 ± 20.1	2.9 ; 0.06
SF-36 role limitations due to physical functioning	22.9 ± 32.9	18.8 ± 28.8	16.3 ± 26.8	2.1 [‡] ; 0.34
SF-36 role limitations due to emotional problems	70.7 ± 42.2	58.3 ± 43.1	63.8 ± 41.3	4.9 [‡] ; 0.09
SF-36 social functioning	51.0 ± 23.3	47.4 ± 20.8	48.9 ± 18.0	1.1 ; 0.3
SF-36 mental health	55.5 ± 17.5	56.8 ± 17.3	57.7 ± 13.9	0.5 ; 0.6
SF-36 vitality	40.6 ± 17.2	36.3 ± 13.7	36.5 ± 12.7	4.5 ; 0.02
SF-36 general health perception	25.0 ± 12.1	25.4 ± 12.9	27.8 ± 14.6	0.6 ; 0.5

VAS=visual analogue scale; CFS-APQ=Chronic Fatigue Syndrome Activities and Participation Questionnaire; SF-36=Medical Outcomes Short Form 36 Health Status Survey; ANOVA=analysis of variances; [‡]Chi-Square value obtained from the non-parametric Friedman analysis

Figure 1. Flow diagram of the study.

