

EVALUATION OF THE EFFECTS OF A TRAINING PROGRAMME FOR PATIENTS WITH PROLONGED FATIGUE ON PHYSIOLOGICAL PARAMETERS AND FATIGUE COMPLAINTS

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Abstract

Objectives: Complaints of prolonged fatigue are considered as a major health problem, as it can affect daily functioning and may lead to work disability. To increase knowledge about the effectiveness of interventions focussing on fatigued patients, a study was designed to evaluate an established training programme for patients with prolonged fatigue. **Materials and Methods:** Eighteen patients who reported fatigue to be one of their major health complaints and who were suffering from functional impairments attended a training programme of six weeks, three times a week. The training consisted mainly of physical endurance training, relaxation therapy and breathing exercises in rest. At baseline, time- and frequency-domain measures of heart rate variability (HRV) and respiration rate measurements were recorded during rest and during recovery after bicycle exercise. Furthermore, fatigue complaints were assessed with the Checklist Individual Strength (CIS). These measurements were repeated at three weeks and six weeks from baseline. **Results:** After three weeks, HRV increased significantly in rest — SDNN, i.e. standard deviation of normal beat-to-beat intervals ($p = 0.02$), very low frequency ($p = 0.04$) and low frequency ($p = 0.04$) — and showed a positive trend in the remaining HRV components. No significant HRV changes during recovery were found. Respiration rate decreased significantly after six weeks during rest (from 11.8, SD = 4.65 to 8.1, SD = 2.57 $\text{b} \times \text{min}^{-1}$) and during recovery (from 15.1, SD = 4.90 to 10.4, SD = 2.97 $\text{b} \times \text{min}^{-1}$). In all patients, CIS scores decreased after six weeks training (from 106, SD = 13.3 to 78, SD = 21.8, $p = 0.001$). **Conclusions:** The results suggest that a six-week training programme has a beneficial effect on physiological and subjective parameters in patients with severe complaints of fatigue.

Key words:

Autonomic nervous system, Heart rate variability, Physiological parameters, Prolonged fatigue, Training programme, Respiration rate

INTRODUCTION

Feelings of fatigue are common complaints among both the general and working population [1–3]. It is a normal phenomenon after physical or mental exertion that usually abates after a period of rest, when tasks are changed or when coping strategies are used [4,5]. Sometimes however,

feelings of fatigue persist. Unlike acute fatigue, prolonged fatigue is not task-specific, does not recover in short term and affects individual's work performance and activities of daily living. This may result in sick leave and/or work disability [6,7]. Compensation mechanisms (e.g. reducing activity) are not successful in this context, and they do not decrease the feeling of fatigue [4].

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To date, researchers have not reached consensus about the aetiology of prolonged fatigue. One hypothesis is that fatigue develops from chronic stress reactions. A 'stress alarm' occurs when an individual experiences stress, for example when job demands are high and coping (i.e. the expectancy of being able to cope and handle the situation with a positive result) is low [8]. This alarm increases wakefulness and alertness (i.e. arousal) and can eventually lead to a dysfunction of the autonomic nervous system, particularly with regard to the sympathetic nerves. Increased sympathetic activity can be identified by increased heartbeats (i.e. decreased heart rate variability (HRV)) [9] and an increased respiration rate [10]. These reactions can be seen as anticipation for action, and cause the body to consume more energy. The amount of glucose, which is used as fuel, increases with activity (e.g. [11]). When the body is in a state of sustained arousal (i.e. extra alert and active for a longer period of time), the energy supply is thus likely to be depleted, possibly leading to fatigue, exhaustion and similar complaints. If they persist, such complaints can provoke problems at work and in the daily routine. Thus, chronic stress, resulting in overactive stress systems (e.g. autonomic nervous system), can lead to long-term adverse physiological effects resulting in prolonged fatigue complaints [12]. The relationship between dysregulation of the autonomic nervous system and chronic fatigue complaints has been reported in several studies [13–15]. Interventions regarding prolonged fatigue have focussed primarily on the cognitive components of stress-related complaints and fatigue [16,17]. Considering those theoretical ideas, it seems that breaking through the vicious circle by means of an intervention aimed at physiological and physical components may provide a number of interesting results. It appears that physiological parameters can be influenced by physical training in normal individuals. In addition, it is clear that physical training has positive effects in terms of increased HRV in healthy individuals [18–20] and in chronic heart failure patients [21–23]. However, the effects of physical training on physiological parameters in patients with complaints of fatigue have not yet been studied.

In this present study an established six-week intervention, consisting of endurance training, relaxation therapy and

breathing exercises is evaluated to answer the following research question: What are the changes in physiological parameters and fatigue feelings in patients with prolonged fatigue after a six week training programme? Fatigue-related complaints were expected to reduce after the intervention. Furthermore, the training was expected to have beneficial effects on physiological parameters (i.e. it raises HRV, while lowering respiration rate) at rest and during recovery after exercise. Both parameters were measured to see if physiological responses occur when they are not needed (i.e. in rest) and to find out if patients recuperate after physical activity (i.e. during recovery).

MATERIALS AND METHODS

Patients

The patients were recruited from among new clients of an outpatient clinic for rehabilitation and medical fitness (Energy Control, Weesp, the Netherlands). Clients (self-referred) who wanted to attend a training at the outpatient clinic, were asked to participate in the current study when they met the following inclusion criteria: 18 to 65 years of age, prolonged complaints of fatigue as a main or important problem and suffering from functional impairments (e.g. constraints in everyday life). Patients who reported a somatic condition (e.g. cancer, HIV, multiple sclerosis or chronic obstructive pulmonary disease) which could explain fatigue complaints were excluded from participating in the study. All patients were enrolled within a period of five months.

Information about personal characteristics was collected, including the duration and subjective reasons for the complaints of fatigue. At the same time, patients were asked about their activities in both work and home setting. A written informed consent was obtained from each participant in this study.

Previously collected pre- and post-HRV data from the outpatient clinic were used to estimate the effect-sizes and determine the sample-size of this study by a power analysis programme (G*POWER) [24]. Fifteen patients were necessary to obtain a power value of 0.82 and an alpha of 0.05. A decision was made to include a total number of 16 patients.

Protocol

A pre-post design with repeated measurements, at baseline and at three and six weeks after baseline was used. On the assessment days, patients completed a questionnaire concerning their fatigue complaints. Secondly, patients remained in a sitting rest position, while heart rate and respiration signals were recorded for ten minutes, using the Co2ntrol recording device (Decon Medical Systems, Weesp, the Netherlands). Adhering to the test procedure of the clinic, patients performed a peak exercise test (see further below). The procedure ended with a recovery phase of ten minutes in sedentary position on the bicycle, while heart rate and respiration signals were recorded.

Intervention

Prior to the above mentioned recovery phase, patients performed a peak exercise test on a bicycle-ergometer (EC-Bike 1000WS) to determine their physical status. This test, carried out by an exercise instructor, is part of a physical examination which the outpatient clinic uses to prepare a personal training programme. All patients who participated in the pilot study performed the exercise test.

Patients were not allowed to eat, or drink coffee for two hours before the bicycle exercise test. All tests were performed using a standardized exercise test at the same time of day before and after the training period of three and six weeks. The workload was increased at a rate of $10 \text{ W} \times \text{min}^{-1}$ for women and $20 \text{ W} \times \text{min}^{-1}$ for men, both starting with unloaded pedalling. The patients were instructed to continue pedalling at a rate of 70–75 rpm until volitional exhaustion. After the subjective maximum had been reached, patients remained cycling for five minutes at a resistance of 40% of their maximum performed load, in order to cool down. During the test, heart rate and respiration signals were recorded by the Co2ntrol recording device (Decon Medical Systems, Weesp, the Netherlands). The aerobic threshold (i.e. respiration rate of $30 \text{ times} \times \text{min}^{-1}$ and estimated Respiratory Quotient (RQ) ($\dot{V}\text{CO}_2/\dot{V}\text{O}_2$) of approximately 1.00) was determined individually during the exercise test, using data from the Co2ntrol recordings (i.e. respiration rate, inhalation and exhalation time and chest extension).

A personal workout schedule was made based on the results of the peak exercise test. Heart rate limits thought to be corresponding to RQ-measures were used as references, and patients were provided with heart-rate monitors (Polar Electro) to monitor these limits during physical exercises. This personalized workout scheme was meant to ensure optimal training and prevent overload and increasing complaints of fatigue.

The training programme comprised three two-hour sessions per week for a period of six weeks, and each session consisted of:

- ‘Passive’ warming up for 15 minutes: Patients receive a massage (through a massage mattress), magnetic-field therapy and infrared therapy in supine position, to increase body temperature.
- ‘Active’ warming up for six minutes: Patients ride a bicycle at an intensity corresponding to an RQ of 0.70 and respiration rate up to $22 \text{ times} \times \text{min}^{-1}$, in order to increase muscle temperature. During this exercise, extra oxygen (up to 35%) is applied through a nasal tube.
- Exercises on the bicycle for 20 minutes, to increase aerobic fitness: The intensity corresponds to an RQ of 0.85 and respiration rate between 22 and $26 \text{ times} \times \text{min}^{-1}$. During this exercise, extra oxygen (up to 35%) is applied through a nasal tube.
- Exercises (walking or rowing) for six minutes, to increase aerobic fitness: This exercise is performed at an intensity corresponding to an RQ of 0.93 and respiration rate between $26 \text{ and } 30 \times \text{min}^{-1}$.
Strength exercises on a vibration platform (Power Plate® International, Badhoevedorp, the Netherlands) for a maximum of 20 minutes: seven exercises to strengthen the lower extremity (e.g. the buttocks, hamstrings, quadriceps and calves muscles). During each 30-second exercise, the vibrations are set to a speed of 30 to 40 times per second. The frequency of the vibration platform during the exercises is 35 Hz, with amplitude between 2 mm (20% of the exercises) and 4 mm (80% of the exercises), in a vertical direction.
- ‘Active’ cooling down for six minutes: Patients ride the bicycle at an intensity corresponding to an RQ of 0.70 and respiration rate up to $22 \text{ times} \times \text{min}^{-1}$, to decrease

muscle temperature and remove residual products from the muscles.

- Breathing exercises for 15 minutes, monitored by Co2ntrol output, in order to provide visual feedback. Breathing exercises consist of practising a relaxing respiratory pattern: two seconds of inhalation, four seconds of exhalation and two seconds waiting before the next inhalation. This is thought to bring about an even breathing pattern and relaxation. Practising this respiration pattern was given as homework.
- ‘Passive’ cooling down for 15 minutes: Patients receive a massage (through a massage mattress), magnetic-field therapy and infrared therapy in supine position for faster and better total recovery.

The workload of this programme increased each week: the 20-minute exercises increased by four minutes each week, while the exercise intensity remained at an RQ of 0.85. After three weeks, the training programme was evaluated (using the exercise test) and adjusted when necessary.

Data collection

Fatigue

The Checklist Individual Strength (CIS), [25] was used to measure fatigue. The CIS consists of 20 statements that cover several aspects of fatigue. Each item is scored on a 7-point Likert scale (1 = Yes, that is true; to 7 = No, that is not true). The scores range from 20 to 140 and a total score can be calculated by adding all item scores. Higher score indicates a higher severity of fatigue complaints [25]. The CIS was found reliable ($\alpha = 0.90$) [25] and the scale has been validated in the Dutch working population [26].

Physiological measures

Heart rate variability and respiration rate measurements were determined from the data collected following the protocol described above. These physiological measurements were recorded using the Co2ntrol (Decon Medical Systems, Weesp, the Netherlands), a small and light device which is attached to a chest strap. The Co2ntrol detects R-tops of the QRS complexes in the beat-to-beat heart rate signal. The normal-to-normal (NN) intervals (i.e. the normal RR intervals between adjacent QRS complexes)

are determined from these R-tops with an accuracy of 1 ms. Time-domain and frequency-domain (HRV) measurements were calculated from these NN intervals. The elastic chest strap, which the Co2ntrol is attached to, records chest expansion. To measure respiration rate, inhalation and exhalation times, chest extension and breathing signals are logged every 1 ms from these records.

The Co2ntrol was developed according to the guidelines of the European and North American Task Force [27]. It was found to provide reproducible HRV and respiration rate measurements in both healthy individuals [28] and in patients with prolonged fatigue (Guijt, Sluiter and Frings-Dresen, 2006; unpublished observation).

Data analysis

Data reduction

Heart rate variability (HRV) was assessed by means of i) time-domain characteristics; the standard deviation of NN intervals (SDNN) and the square root of the mean of the sum of squares of differences between adjacent NN intervals (RMSSD) and ii) frequency-domain characteristics; very low frequency (VLF) (0.003–0.05 Hz), low frequency (LF) (0.05–0.15 Hz), high frequency (HF) (0.15–0.4 Hz) and the ratio between low frequency and high frequency (LF:HF ratio), according to the guidelines of the European and North American Task Force [27]. To determine these measurements, data were transferred to HRV Analysis Software (<http://venda.uku.fi/research/bisignal>) [29]. The Fast Fourier transform (FFT) option was used to determine the spectrum of HRV and RR series were re-sampled at a rate of 4 Hz using cubic interpolation. To determine rest values, the final seven minutes of the ten minute recording period in sedentary resting position were selected. To determine recovery values, the final five minutes of the ten minute recording period during the recovery phase were selected. The same data selection was used to determine the respiration rate.

Statistical analysis

To assess the changes in physiological parameters and fatigue feelings after a six week physical training, analysis of variance between the measurements at baseline (t_0),

at three weeks (t1) and six weeks (t2) from baseline was conducted. Differences in the variables (i.e. rest and recovery values of HRV and respiration rate and the fatigue score) were compared using the General Linear Models procedure for repeated measurements. A post-hoc multiple-comparisons procedure was followed to test significant differences between test moments. Values of $p < 0.05$ were considered statistically significant. The statistical analyses were performed using SPSS version 12.0.1 for Windows (SPSS Inc., Chicago, IL, USA). In addition, the results of the physiological characteristics were described separately for men and women.

RESULTS

Personal characteristics

Eighteen patients (7 men and 11 women) were included in the sample. Ages varied between 20 and 63 years (mean = 48 years, SD = 11.8). At baseline, two patients were working full-time, three worked part-time and 13 were unemployed. Sixteen out of 18 patients completed the entire six-week training programme. Two patients dropped out, one because of back problems and one because of lack of motivation. The mean number of training sessions was 17 (SD = 1.0) in the six-week period, with a frequency of approximately three sessions a week.

Table 1. Number of patients (men and women), mean values, standard deviations (SD) and p-values before (baseline) and after treatment (three and six weeks) on heart rate variability (SDNN, RMSSD, VLF, LF, HF and LF:HF ratio), respiration rate and fatigue, based on General Linear Model (GLM) analysis

Variable	N	Baseline (t0)	Three weeks from baseline (t1)	Six weeks from baseline (t2)	GLM
		Mean (SD)			Overall <i>p</i> -values
HRV rest					
SDNN (ms)	16	29 (12.0)	39 (23.4)*	40 (23.6)*	.02
RMSSD (ms)	16	21 (12.2)	26 (15.4)	30 (19.1)	.07
VLF (ms ²)	16	56 (34.3)	53 (36.6)	88 (77.5)*	.04
LF (ms ²)	16	318 (280.9)	761 (895.0)*	809 (989.4)*	.04
HF (ms ²)	16	104 (99.9)	144 (181.5)	138 (117.2)	.55
LF:HF (%)	16	4.8 (3.86)	6.6 (5.84)	5.6 (3.86)	.12
HRV recovery					
SDNN (ms)	16	12 (5.1)	13 (8.3)	13 (8.4)	.69
RMSSD (ms)	16	6 (2.9)	7 (4.9)	6 (4.8)	.28
VLF (ms ²)	16	20 (22.8)	18 (27.4)	12 (8.8)	.46
LF (ms ²)	16	54 (40.2)	97 (129.7)	95 (126.8)	.18
HF (ms ²)	16	9 (12.6)	24 (54.0)	19 (43.4)	.30
LF:HF (%)	16	9.9 (7.08)	12.3 (12.35)	9.2 (8.16)	.60
Respiration Rate rest (breaths×min ⁻¹)	14	11.8 (4.65)	8.8 (3.89)*	8.1 (2.57)**	.001
Respiration Rate recovery (breaths×min ⁻¹)	14	15.1 (4.90)	10.4 (3.38)*	10.4 (2.97)*	.001
Fatigue (total CIS score, range 20–140)	16	106 (13.3)	87 (22.5)***	78 (21.8)***	.001

HRV rest — heart rate variability during rest.

HRV recovery — heart rate variability during recovery.

SDNN — standard deviation of NN intervals.

RMSSD — square root of the mean of the sum of squares of differences between adjacent NN intervals.

VLF — very low frequency (0.003–0.05 Hz).

LF — low frequency (0.05–0.15 Hz).

HF — high frequency (0.15–0.4 Hz).

Post-hoc analysis within subjects (compared to t0): * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Heart rate variability

As shown in Table 1, the mean resting SDNN values increased significantly ($p = 0.02$) from 29 ms (SD = 12.0) at baseline to 39 ms (SD = 23.4) after three weeks, and to 40 ms (SD = 23.6) after six weeks. Post-hoc analysis showed that changes between baseline and three weeks and between baseline and six weeks were significant (not shown in Table 1: both $p = 0.03$).

There was no significant difference between baseline and follow-up tests on RMSSD rest values ($p = 0.07$).

Two out of three frequency-domain characteristic showed significant results: VLF power in rest increased from 56 ms² (SD = 34.3) at baseline to 88 ms² (SD = 77.5) after six weeks. Post-hoc analysis showed a significant change between baseline and six weeks ($p = 0.05$). LF power in rest increased from 318 ms² (SD = 280.9) to 809 ms² (SD = 989.4) after six weeks with post-hoc tested significant changes between baseline and three weeks and six weeks ($p = 0.03$ and $p = 0.05$ respectively). Furthermore, in rest, HF power increased non-significantly from 104 ms² (SD = 99.9) to 138 ms² (SD = 117.2) after six weeks. The LF:HF ratio increased, but the changes were not significant.

As for the recovery measurements, neither frequency-domain parameters nor time-domain parameters did show significant changes between baseline and follow-up tests (Table 1).

Respiration rate

The mean rest respiration rate values decreased significantly ($p = 0.001$) from 11.8 breaths \times min⁻¹ (SD = 4.65) to 8.8 breaths \times min⁻¹ (SD = 3.89) after three weeks, and to 8.1 breaths \times min⁻¹ (SD = 2.57) after six weeks from baseline. Post-hoc analysis showed that the difference between baseline and three weeks was significant ($p = 0.014$), as was the difference between baseline and six weeks ($p = 0.003$) (Table 1).

The mean recovery respiration rate values also changed significantly ($p = 0.001$) between the three measurement points, with mean values from 15.1 breaths \times min⁻¹ (SD = 4.90)

to 10.4 breaths \times min⁻¹ (SD = 3.38) after three weeks, and to 10.4 breaths \times min⁻¹ (SD = 2.97) after six weeks. The p -values between baseline and three weeks and between baseline and six weeks were both 0.001 (Table 1).

Fatigue

Duration of fatigue complaints ranged from six months to 22 years at the start of the training. Twenty-two percent of all patients attributed their complaints to work characteristics; 11% reported that the complaints had been caused by private psychosocial factors, 50% reported that a combination of these two factors caused their symptoms and 6% attributed their symptoms to something else.

Significant differences in mean CIS scores, which represent fatigue complaints, were found between the three measurements in time. A significant decrease ($p = 0.001$) of the mean fatigue values was noted, from 106 (SD = 13.3) at baseline, to 87 (SD = 22.5) after three weeks, and to 78 (SD = 21.8) after six weeks. Post-hoc analysis showed that the differences were significant across all three groups. The p -value between baseline and three weeks was 0.001, and between baseline and six weeks, the value was also $p = 0.001$ (Table 1).

To give an impression on how gender may have influenced the results, the results of HRV and respiration rate analysis are described separately for women and men in Table 2 and 3, respectively.

DISCUSSION

The main results of this pilot study suggest that after physical training, patients with fatigue complaints experience beneficial changes in HRV, respiration rate and fatigue. A significant increase in HRV (determined by rest SDNN, VLF and LF indices) was observed after the training. A trend towards increased HRV was found in the remaining HRV rest values. Non-significant changes in HRV recovery values were found in rest after the training. Thus, beneficial HRV changes can be observed in rest, but patients did not recover faster from physical exertion after six weeks training. To our knowledge, few if any studies

Table 2. Number of patients (women), mean values and standard deviations (SD) before (baseline) and after treatment (three and six weeks) on heart rate variability (SDNN, RMSSD, VLF, LF, HF and LF:HF ratio) and respiration rate

Variable	N	Baseline	Three weeks from baseline	Six weeks from baseline
		(t0)	(t1)	(t2)
Mean (SD)				
HRV rest				
SDNN (ms)	11	32 (11.5)	46 (24.0)	46 (24.5)
RMSSD (ms)	11	24 (12.7)	31 (15.6)	35 (20.1)
VLF (ms ²)	11	60 (34.3)	58 (38.7)	84 (72.3)
LF (ms ²)	11	382 (302.9)	1038 (961.8)	1046 (1104.2)
HF (ms ²)	11	127 (107.0)	183 (206.7)	166 (122.1)
LF:HF (%)	11	4.6 (3.69)	7.4 (6.18)	6.2 (4.34)
HRV recovery				
SDNN (ms)	11	13 (5.5)	13 (7.5)	13 (8.0)
RMSSD (ms)	11	6 (3.1)	6 (4.0)	6 (4.5)
VLF (ms ²)	11	23 (26.1)	15 (26.0)	13 (9.3)
LF (ms ²)	11	55 (41.0)	92 (97.7)	95 (114.2)
HF (ms ²)	11	10 (13.8)	13 (20.2)	10 (11.0)
LF:HF (%)	11	9.2 (7.03)	12.9 (11.96)	8.6 (8.57)
Respiration Rate rest (breaths×min ⁻¹)	10	10.3 (4.21)	6.7 (1.56)	6.9 (1.37)
Respiration Rate recovery (breaths×min ⁻¹)	10	13.5 (4.32)	9.0 (2.43)	9.5 (2.16)

Abbreviations as in Table 1.

have investigated the effects of physical training in patients with complaints of fatigue. Nonetheless, the results of several previous studies that used different populations are consistent with our present results [18,21]. These studies showed increased HRV (SDNN, HF, LF, and/or LF:HF ratio components) after physical training in healthy individuals and in chronic heart failure patients.

HRV components: SDNN, RMSSD and HF power are known to be mediated by vagal activity and an increase of these components therefore indicates an increase of parasympathetic activity [23,30]. The interpretations of LF power and LF:HF ratio are somewhat controversial. The ratio between LF and HF power is the sympathovagal balance, but lacks physiological base [20]. LF power is by some considered as a mediator of both the parasympathetic and sympathetic nervous system [27]. The increased LF power found in this study may seem in contrast with this explanation, but has been found before by Sandercock et al. after

eight weeks of cardiac rehabilitation [23]. As for the VLF component, a significant change was observed after the six weeks training period. However, physiological interpretation can not be made, since VLF power is a dubious measure [27].

Large variations in individual effects were found within and between genders (Table 2 and 3), especially in the LF and HF power components. Post-hoc analyses showed that the individual LF power differences in women between baseline and six weeks training ranged from -180 ms² to 3439 ms². In men, individual changes between baseline and six weeks training ranged from -32 ms² to 425 ms². Additional analysis of the HF power component showed relatively even larger individual differences within men and women. These differences were partly due to some extreme values but may have influenced the results since previous studies found that aging is associated with a reduction in parasympathetic control and that autonomic

Table 3. Number of patients (men), mean values and standard deviations (SD) before (baseline) and after treatment (three and six weeks) on heart rate variability (SDNN, RMSSD, VLF, LF, HF and LF:HF ratio) and respiration rate

Variable	N	Baseline	Three weeks from baseline	Six weeks from baseline
		(t0)	(t1)	(t2)
Mean (SD)				
HRV rest				
SDNN (ms)	5	22 (10.9)	22 (10.3)	27 (17.1)
RMSSD (ms)	5	14 (7.8)	15 (9.1)	18 (11.6)
VLF (ms ²)	5	47 (36.8)	41 (32.1)	99 (96.1)
LF (ms ²)	5	177 (174.8)	151 (117.6)	287 (356.8)
HF (ms ²)	5	54 (65.3)	57 (54.9)	76 (85.9)
LF:HF (%)	5	5.2 (4.63)	5.0 (5.24)	4.2 (2.31)
HRV recovery				
SDNN (ms)	5	10 (4.4)	13 (10.8)	12 (10.2)
RMSSD (ms)	5	4 (2.1)	9 (6.7)	6 (6.2)
VLF (ms ²)	5	14 (13.4)	23 (32.9)	9 (7.8)
LF (ms ²)	5	54 (42.9)	110 (197.3)	93 (166.3)
HF (ms ²)	5	7 (10.7)	47 (94.8)	37 (78.3)
LF:HF (%)	5	11.6 (7.69)	10.9 (14.52)	10.4 (7.95)
Respiration Rate rest (breaths×min ⁻¹)	4	15.6 (3.81)	14.0 (2.68)	11.2 (2.26)
Respiration Rate recovery (breaths×min ⁻¹)	4	19.1 (4.25)	13.7 (3.27)	12.6 (3.88)

Abbreviations as in Table 1.

differences are gender-specific [20]. However, in this study, no indications of even intermediate correlations between age and gender and any HRV component and respiration measurement were found after post-hoc analysis. Because of the small number of subgroups of patients included in this study, we did not test these indications statistically.

As hypothesized, the second physiological parameter, respiration rate, decreased significantly. The results show that, with the exception of two individuals, the respiration rate of all patients decreased both during rest and during recovery after physical exertion. A possible explanation is consistent with the authors' hypothesis: chronic stress reactions, which were assumed to occur in this population, might have been reduced due to relaxation, exercise or a combination of the two. The reduction of chronic stress reactions may decrease the stress alarm and thereby reduce the sympathetic activity. In combination with the relaxing breathing impulses that are given during the breathing exercises,

patients might have been able to decrease their respiration rate. An alternative explanation for the findings is that the decreases in respiration rate were due to the combination of breathing exercises with physical training, which was an important component of the programme.

A significant decrease in fatigue symptoms was found. All patients experienced fewer complaints at the end of the intervention period, compared to baseline. At baseline, a mean CIS score over 100 was found. This score was only slightly lower than the total CIS score of patients with chronic fatigue syndrome (mean = 113) [25], but higher than the total score for patients reporting mental reasons for fatigue (mean = 90) [26]. Furthermore, the personal CIS scores are also worth mentioning. At baseline, all patients had CIS scores above 76 (range from 86 to 129), which was determined as the cut-off point for chronic fatigue [31]. This cut-off point can be associated with increasing risk level for sick leave or work disability. After

three weeks, the scores of four out of 16 patients were below the cut-off point; after six weeks, six patients had scores of 74 or lower. In other words, all patients reported less fatigue symptoms after the six-week training period, and the complaints decreased in one quarter of the cases from severe to moderate.

The existing training programme that was evaluated in this study consists primarily of endurance training and breathing exercises. Several other components were part of the programme as well, including magnetic field therapy, infrared therapy, power-plate exercises and application of extra oxygen. The effectiveness of these solo components is unclear. However, they are part of the original training programme of the outpatient clinic and were, therefore, not excluded.

The following limitations should be taken into account. First, no control group was included in this evaluation study. Thus, it is not possible to ascribe all of the observed results to the intervention. However, the patients reported to have their complaints for long periods of time and no other intervention took place during the study period. A second limitation may be found in the short duration of the intervention. A longer training period may produce greater physiological changes and additional follow-up measures can provide more information about long-term effects. Therefore, it is suggested to extend the training programme duration to follow-up physiological effects after a longer intervention period. Furthermore, due to the small number of subgroups of patients included in this study, we were not able to perform separate analysis for men and women. In future studies, when more patients can be included, it is suggested to present the data according to gender and take age into account. In the end, it might be interesting to study the effects of a physical training programme on return-to-work in future research, since a majority of the patients participating in this study were unemployed.

CONCLUSION

The results of the current study suggest that a six week physical training improves heart rate variability and respiration rate in patients with complaints of prolonged fatigue. Furthermore, patients reported a significant and

clinically relevant decrease in fatigue complaints after the training programme. These results seem promising for successful treatment of patients with prolonged and severe fatigue complaints.

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