Multiple Sclerosis and Exercise Program Intensity

Effects of a Short Physical Exercise Interventions on Patients with Multiple Sclerosis (MS)

Keywords: endurance training; resistance training; VO_{2peak}; VAT; quality of life; MFIS; SF36

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease and is associated with reduced physical capacity and quality of life (Qol) [1,2]. Today, it is known that physical exercise does not lead to relapse or a faster progression of the disease but decreases fatigue and improves fitness, Qol [3–8], and walking ability in particular walking speed and endurance [9]. Despite these facts, patients with MS have been reported to undertake less sporting activity than the normal population [10], resulting in reduced physical capacity [11]. This sedentary lifestyle in patients with MS is mainly caused by deficits of the musculoskeletal system but also by psychosocial factors, such as loss of enjoyment of exercise, a lack of belief in the success of training or fear of relapse [10,12].

More than half of the patients with MS have been reported to suffer from heat sensitivity, which results in a reversible worsening of MS symptoms, for example, when participating in physical activities [13]. Since resistance training leads to a lesser increase in the core temperature than endurance training, it is better tolerated for heat-sensitive patients with MS [14].

In general, inadequate levels of physical fitness lead to higher cardiovascular and general mortality [15]. Additionally, deficient cardiopulmonary fitness is an important cardiovascular mortality risk factor and even more significant than classical risk factors, such as diabetes mellitus, overweight, smoking and hypercholesterolemia [16]. In this regard, it is necessary, especially for patients with MS and low physical fitness, to improve their physical fitness.

Wens I. *et al.* [17] found a smaller mean cross sectional area (CSA) of all muscle fibers as well as a smaller CSA of type I, II and IIa fibres of the quadriceps in 34 patients with MS, resulting in a lower muscle strength of the lower limb compared to healthy controls. A systematic training program can counteract this deconditioning caused by inactivity.

The World Health Organization recommends 150 min of moderate-intensity activity per week for healthy adults [18]. However, these recommendations are difficult to implement for patients with MS.

Physical limitation of patients with MS is mainly caused by decreased VO_{2max} and reduced muscle strength [1,19]. Therefore, in this prospective randomized trial, two different training regimes (an endurance and a combined endurance/resistance training program) were compared to investigate their effects on aerobic capacity and maximum force in patients with mild to moderate MS in short physical exercise units (two times a week, for forty minutes). Additionally, we evaluated the effects of the programs on fatigue and Qol as secondary outcomes. We hypothesized that the endurance program has more significant effects on aerobic capacity while the combined program has a better effect on maximum force.

2. Results

Between the baseline examination and the end of the training program, 18 patients dropped out because of personal reasons unrelated to the intervention (lack of time, new workplace, long distance to the location of the training). Five patients (8%) experienced an exacerbation of MS symptoms before completing the training program. Overall, 23 patients (38%) were excluded for the sensitivity analysis (Figure 1).

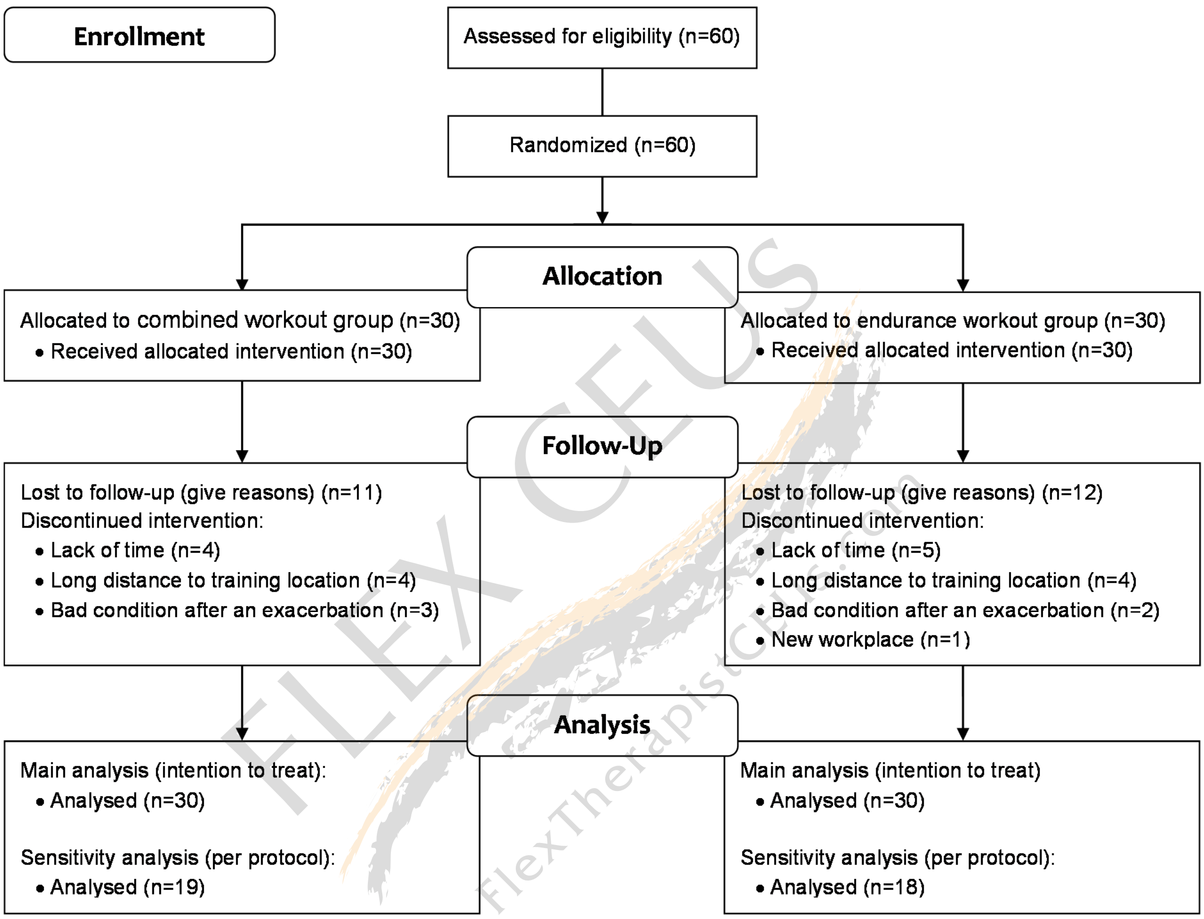

Figure 1. Flow chart of drop outs.

2.1. Aerobic Capacity

Both groups were comparable in age, BMI, sex, and intensity of the MS (Table 1). Additionally there was no significant difference between both groups concerning load (W) ($p = 0.69$), VO_{2peak} (mL/min/kg_{BW}) ($p = 0.85$) and VAT (W) ($p = 0.68$) (Table 2).

Aerobic capacity, as demonstrated by the parameters listed below, was significantly higher in both groups after training, but there was no significant difference between the two training types (Table 2). After training, both groups improved their parameters of physical capacity (Figure 2a); there was no significant time × group effect. Although, in the case of VO_{2peak}, the main analysis showed no significant time effect, the sensitivity analysis revealed a significant improvement over time in both groups (VO_{2peak} in mL/min $p < 0.01$, $\eta^2 = 0.39$ respectively in mL/min/kg_{BW} $p < 0.01$, $\eta^2 = 0.37$) with no differences between groups ($p = 0.96$ respectively $p = 0.72$).

Table 1. Baseline characteristics.

Parameter	CWG (n = 30)	EWG (n = 30)	p-Value
Age (years)	42.3 ± 9.0	45.6 ± 11.4	0.21
Height (cm)	170 ± 5	169 ± 4	0.66
Body weight (kg)	71.4 ± 12.1	70.8 ± 11.9	0.84
BMI (kg/m^2)	24.5 ± 3.6	24.7 ± 4.0	0.86
EDSS	2.6 ± 1.1	3.1 ± 1.3	0.09
MS specific medication	20/30	21/30	
Female/male	24/6	20/10	

Values are mean ± SD.

Table 2. Physical capacity parameters at baseline and after training (T2).

Parameter	CWG		EWG		p-Value		
	Baseline	T2	Baseline	T2	Time	η^2	Time × Group
Load (W)	124 ± 48	131 ± 53	119 ± 44	124 ± 41	<0.01	0.17	0.78
Load (W/kg)	1.75 ± 0.61	1.84 ± 0.68	1.71 ± 0.66	1.78 ± 0.60	<0.01	0.17	0.78
Lactate$_{50W}$ (mmol/min)	1.45 ± 0.51	1.31 ± 0.51	1.57 ± 0.79	1.35 ± 0.52	<0.01	0.14	0.54
Lactate$_{max}$ (mmol/min)	5.43 ± 2.03	5.90 ± 1.97	4.80 ± 2.89	5.14 ± 2.50	<0.01	0.12	0.66
Heart rate$_{rest}$ (bpm)	92 ± 12	90 ± 11	88 ± 12	85 ± 13	0.02	0.09	0.63
Heart rate$_{50W}$ (bpm)	120 ± 15	115 ± 15	116 ± 15	110 ± 14	<0.01	0.31	0.74
Heart rate$_{max}$ (bpm)	161 ± 17	162 ± 18	152 ± 24	152 ± 24	0.53	–	0.85
VO_{2peak} (mL/min)	1684 ± 601	1756 ± 599	1632 ± 539	1676 ± 494	0.12	–	0.71
VO_{2peak} (mL/min/kg$_{BW}$)	23.8 ± 7.8	24.6 ± 7.4	23.5 ± 8.2	23.7 ± 7.1	0.24	–	0.72
Borg scale	16.5 ± 1.4	16.0 ± 1.9	16.3 ± 1.4	15.7 ± 1,70	0.02	0.09	0.68
VAT (W)	51.0 ± 23.4	55.8 ± 24.8	50.5 ± 23.1	57.6 ± 25.5	<0.01	0.26	0.39
VAT (mL/min/kg$_{BW}$)	12.8 ± 3.3	13.7 ± 3.4	13.3 ± 4.3	14.2 ± 4.4	<0.01	0.35	0.79

Values are mean ± SD; VO_{2peak}, peak oxygen uptake; BW, body weight; VAT, ventilatory anaerobic threshold.

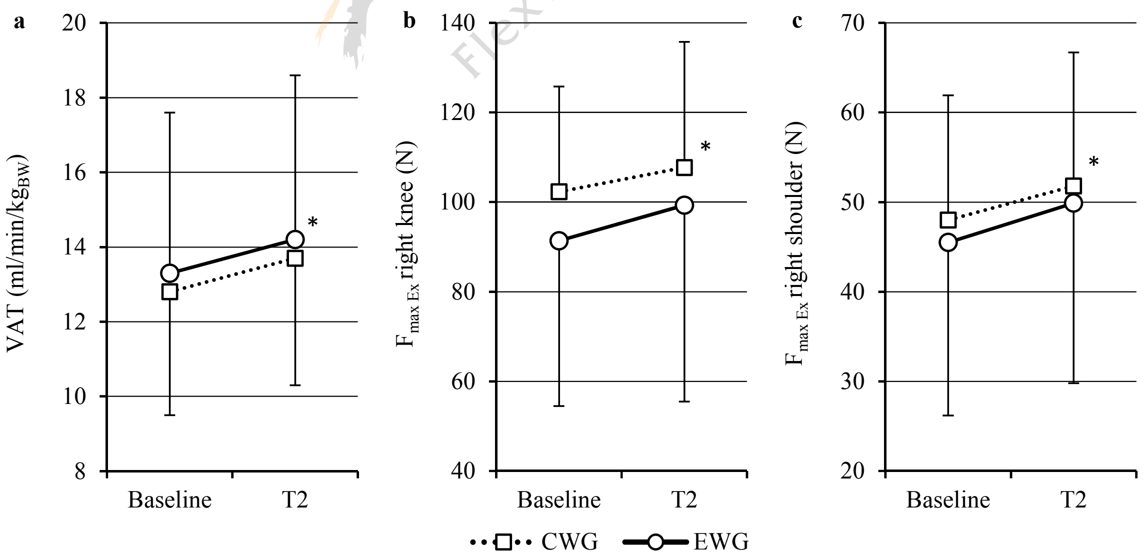

Figure 2. Ventilatory anaerobic threshold (**a**), maximum force for the right knee (**b**) and shoulder extensors (**c**) at baseline and after training (T2). * p < 0.01 over time in both groups with no differences between groups.

The spiroergometric tests were stopped by the patient with the onset of subjective exertion with an average value of 16 on the Borg scale, with no significant differences in maximal heart rate in both groups over time and between the two training types (Table 2). Additionally there was no significant change in the EDSS over time in both groups (CWG: 2.6 + 1.1, 2.6 + 1.1; EWG: 3.1 + 1.3, 3.1 + 1.3; p = 0.16).

2.2. Isokinetics

Measurements of F_{max} for the knee flexors (FL, hamstrings) and extensors (EX, quadriceps femoris), as well as for the shoulder extensors and flexors, showed significantly higher results for both the left- and right-hand side after the training period (Figure 2b,c) with the exception of $F_{max\ Ex}$ left (Table 3). Again, there was no significant difference between the types of training. The sensitivity analysis of $F_{max\ Ex}$ of the left knee showed significantly higher values after training (p = 0.01, η^2 = 0.18) with no differences between groups (p = 0.82).

Table 3. Isokinetic parameters at baseline and after training (T2).

Parameter	CWG		EWG		*p*-Value		
	Baseline	**T2**	**Baseline**	**T2**	**Time**	**η^2**	**Time × Group**
Knee							
$F_{max\ Ex}$ right (N)	102.3 ± 23.5	107.7 ± 28.0	91.4 ± 36.9	99.3 ± 42.3	<0.01	0.15	0.50
$F_{max\ Ex}$ left (N)	105.5 ± 28.1	108.2 ± 33.1	92.7 ± 39.3	95.6 ± 43.8	0.23	-	0.95
$F_{max\ Fl}$ right (N)	55.3 ± 16.0	61.3 ± 18.7	51.0 ± 21.0	55.9 ± 24.6	0.01	0.18	0.72
$F_{max\ Fl}$ left (N)	58.2 ± 20.2	64.0 ± 23.7	48.7 ± 23.5	51.7 ± 24.85	<0.01	0.16	0.31
Shoulder							
$F_{max\ Ex}$ right (N)	48.0 ± 13.9	51.8 ± 14.9	45.5 ± 19.3	49.9 ± 20.1	<0.01	0.14	0.85
$F_{max\ Ex}$ left (N)	46.3 ± 17.5	50.0 ± 18.9	43.3 ± 17.3	46.9 ± 18.6	<0.01	0.19	0.98
$F_{max\ Fl}$ right (N)	34.2 ± 9.6	36.5 ± 10.0	35.3 ± 12.6	36.9 ± 14.1	0.02	0.10	0.67
$F_{max\ Fl}$ left (N)	35.8 ± 13.9	36.9 ± 12.4	34.0 ± 12.1	35.9 ± 12.5	0.04	0.07	0.60

Values are mean ± SD. Ex, extensor; Fl, flexor.

2.3. Questionnaires

2.3.1. SF-36

Both groups showed significantly better results for the subscales 2, 4, 5, 6 and 8 and for the mental health sum score at the end of the study (Table 4).

2.3.2. MFIS

In both groups, we found a significant reduction of the fatigue score for all patients (Table 4) as well as for the patients with a pathological score over 38 (n = 17; 52 ± 8 before training, 42 ± 11 after training; p < 0.001).

2.4. Training Program

Overall more than 90% of the training sessions (on average 24/26) were completed.

Table 4. Questionnaire parameters at baseline and after training (T2).

Parameter	CWG		EWG		*p*-Value		
	Baseline	T2	Baseline	T2	Time	η^2	Time × Group
MFIS score	35.5 ± 17.0	30.6 ± 16.7	35.1 ± 17.4	30.3 ± 18.1	<0.01	0.24	0.97
SF 36							
Scale 1 (physical functioning)	71.7 ± 21.3	71.5 ± 22.9	60.7 ± 27.1	62.7 ± 26.6	0.43	–	0.33
Scale 2 (role limitations due to physical limitations)	50.0 ± 44.9	62.5 ± 42.3	42.1 ± 47.2	50.0 ± 42.0	0.03	0.10	0.63
Scale 3 (bodily pain)	87.9 ± 19.6	87.4 ± 17.4	71.3 ± 24.4	72.4 ± 23.7	0.90	–	0.67
Scale 4 (general health perceptions)	46.9 ± 19.3	49.6 ± 22.4	43.6 ± 24.0	48.8 ± 25.6	0.03	0.10	0.48
Scale 5 (vitality)	47.5 ± 18.7	49.0 ± 20.4	44.8 ± 23.8	50.7 ± 22.3	<0.01	0.18	0.07
Scale 6 (social functioning)	72.9 ± 28.9	76.6 ± 24.3	68.2 ± 30.6	80.1 ± 24.3	<0.01	0.21	0.07
Scale 7 (role limitations caused by emotional problems)	66.7 ± 48.2	65.3 ± 52.5	78.8 ± 40.6	90.9 ± 25.6	0.36	–	0.25
Scale 8 (mental health)	65.8 ± 20.7	67.2 ± 19.1	62.0 ± 20.1	67.8 ± 18.0	<0.01	0.17	0.07
Physical health	44.7 ± 9.1	46.2 ± 9.1	39.0 ± 10.8	39.6 ± 11.3	0.16	–	0.56
Mental health	44.9 ± 13.6	45.4 ± 13.4	46.7 ± 11.7	51.4 ± 8.6	0.04	0.09	0.01 (η^2 = 0.13)

Values are mean ± SD.

3. Discussion

Our results suggest that in patients with MS, regular training for 80 min per week, at a moderate intensity, increases aerobic capacity and maximum force-against our hypothesis-independent of the type of training.

3.1. Aerobic Capacity

The subjective perceived exertion measured with the Borg scale was, on average, 16 (between hard and very hard) for both groups, which indicated that cardiopulmonary exertion was not achieved in all patients. This finding is in line with Heine *et al.* [20], who found that only 23% of their patients with low to moderate MS achieved an exertion of 18 or greater on the Borg scale. Nevertheless, our patients improved their endurance capacity both in VO_{2peak} (although the main analysis showed no significant time effect, the sensitivity analysis revealed a significant improvement over time) and VAT, so a motivation-dependent effect seems unlikely. Even taking into account day-to-day variation in patients with MS, our results of an improvement of approximately 10% in VO_{2peak} (in the sensitivity analysis) can be interpreted as a real training effect [21].

A better endurance capacity after the training period was apparent from a lower heart rate at rest and at 50 W and lower lactate values at 50 W in both groups. These results can be explained by a right shift of the lactate performance curve [22]. Baseline levels of VO_{2peak} from all our patients (22 ± 7 mL/min/kg_{BW}) were reduced, compared to healthy persons and are comparable with other studies taking into account the intensity of MS measured with EDSS [1–3]. Interestingly, both training groups increased their aerobic capacity, although the CWG group only performed 40 min per week of aerobic training on a bicycle ergometer.

Mostert and Kesselring [1] found an average increase in oxygen uptake of 12% at the aerobic threshold for 26 patients with MS cycling five times per week, for 30 min, over 3–4 weeks at the VAT under aerobic conditions. However, VO_{2peak} in this patient group was not improved by exercise therapy. Our results showed a significant growth of VO_2 at the VAT and at least in the sensitivity analysis of VO_{2peak}; one possible explanation is that our patients performed their training at a higher intensity in the aerobic-anaerobic transition area. Although higher lactate values can also be a sign of increased motivation or volitional exhaustion at a later time point, the Borg scale was not different after the incremental tests before and after training for both groups. In addition, motivation-independent parameters, such as VAT, lactate at 50 W, and heart rate at 50 W, showed a significant improvement of aerobic capacity. Compared with other endurance training studies in patients with MS, the improvement of VO_{2peak} in our study was less pronounced [2,3]. Patients in a study by Bjarnadottir *et al.* [2] showed an increase in endurance capacity (15% in VO_{2peak} and 18% increase in VAT) after training three times a week for five weeks on a bicycle ergometer. After a training session performed three times a week, for 40 min, on a combined arm and leg ergometer, Petajan *et al.* [3] observed a 22% increase in VO_{2max} after 15 weeks. The lower results in our patients could be explained by the lower frequency or the shorter duration of our training sessions. However, our results suggest that even 40 min of aerobic training per week (in combination with 40 min resistance training) may be enough for poorly-trained persons to improve their aerobic capacity significantly. Although Motl *et al.* [23] reported significant improvements in walking mobility after eight weeks of combined training, to our knowledge we are the first group who describes a benefit on aerobic capacity in a combined exercise program measured with spiroergometric parameters. This is contrary to the results of Romberg *et al.* [24] who found no significant change in aerobic capacity after a 26 week, home-based, combined training.

3.2. Muscle Strength

Surprisingly, participants in both of our training groups enhanced their maximum force for shoulder and knee extensors and flexors with no significant group effect, although the EWG group performed only endurance training. However, some of the participants in the EWG group also used a cross-trainer, a rowing ergometer or an arm ergometer, besides cycling ergometry, so shoulder and knee muscles were trained regularly. Therefore, these patients could have enhanced their results in isokinetic testing. This is in line with the study from Petajan *et al.* [3] who also found an improvement in muscle strength of the upper and lower extremity in a sole endurance training regime.

A recent study from Wens *et al.* [25] showed a significant improvement of a 24-week combined exercise program on muscle strength of the knee extensors and flexors emphasized in the hamstrings. Other combined training studies observed no, or only a modest, effect on muscle strength of quadriceps and hamstrings.

3.3. Quality of Life

Examination of Qol in patients in a study by Bjarnadottir *et al.* [2], which was determined with the SF-36 questionnaire, showed a tendency towards an improvement in five of eight subscales and was significant for subscale 5 (vitality). Mostert and Kesselring's [1] study also showed a significant increase in subscales 5 and 6 (vitality and social function). Our results were in line with these studies and showed a significant improvement in both groups for subscales 2 (role limitations due to physical limitations), 4 (general health perceptions), 5 (vitality), 6 (social functioning) and 8 (mental health), and for the mental health sum score. In addition to training effects, improvement of psychological subscales could be explained by social interaction and social support from peers and therapists. No measurable effect on the physical sum score was seen in the EWG group or in the CWG. This is contrary to the results from Dalgas *et al.* [26], who performed a 12-week progressive resistance training program for patients with MS and a 12-week follow up trial (after twelve weeks, the exercise group continued training without supervision and the control group was offered the same intervention as the exercise group). They found a significant increase in the knee extensor strength and functional capacity score of the lower extremities in both groups after training. A significant increase in the physical sum score and a trend for the mental component of the SF-36 were seen for the exercise group and for the mental sum score in the control group after exercise. Referring to our patients the EDSS average was 3.0 ± 1.3 (in the sensitivity analysis) compared with 3.7 ± 0.9 in the study by Dalgas *et al.* [26]; thus, we assume that there was no effect since our patients were already in a better condition at baseline and a training effect in the physical sum score could only be seen in the patients with a greater level of disability.

3.4. Fatigue

The effect of exercise training on fatigue is inconsistent [6]; some studies performing endurance [27,28], resistance [26] or combined training [29] showed a significant improvement, while others did not [1,3,30]. In some of the studies, not all patients suffered from fatigue, which was also the case in our study. Nonetheless, in our study, for both the patients suffering from fatigue (MFIS > 38) and for the whole group, we found a significant improvement in fatigue, as determined using MFIS (Table 4).

3.5. EDSS

Golzari *et al.* [31] found a significant decrease in the EDSS after eight weeks of training (from 2.1 to 1.7) in women. In that study, IL-17 and IFN-y production also decreased, and they explained the clinical improvement with training-induced anti-inflammatory effects. In contrast, EDSS was stable in both of our groups, which is in accordance with other studies [2,3] which, likewise, showed no significant effect of exercise training on EDSS. A review on this question published by Dalgas and Stenager [32] stated that it is not clearly established if exercise in patients with MS has a disease-modifying effect or not, although there are individual studies indicating this.

3.6. Dropout

Five patients (8%) could not complete the training because of a relapse, taking into account the existing literature we are sure this was not caused by our training intervention. Petajan *et al.* [3] (13% experienced an exacerbation of MS symptoms with similar frequency in the exercise and non-exercise group) (19) and Bjarnadottir *et al.* [2] (dropout rate of 9% and 8% in the exercise and the control groups, respectively, because of a relapse before starting the training) reported a similar dropout rate in their exercise as well as in their non-exercise groups The other dropouts were caused by circumstances unrelated to the intervention (lack of time n = 9, to long distance to training location n = 8 new workplace n = 1, Figure 1).

4. Patients and Methods

4.1. Patients and Study Design

The study initially involved 60 patients (44 females, 16 males), who were recruited directly through the MS Healthcare Center of the Hannover Medical School by practicing neurologists in the region of Hannover, and through the newsletter of the local MS society. The inclusion criteria for participation in the study were diagnosed MS, adult age (18–65 years), and mobility with a maximum value of 6 (low to moderate disability) on the Expanded Disability Status Scale (EDSS). Inclusion in the study was not influenced by MS specific medication (e.g., Glatirameracetat, Interferon Natalizumab). Reasons for exclusion were additional cardiovascular and orthopaedic diseases, pregnancy and regular physical training over the previous 12-month period. The patients were randomized after an initial examination by age, sex, Body Mass Index (BMI) and EDSS into either the combined workout group (CWG) or the endurance workout group (EWG). Spiroergometry, isokinetics, a neurological examination, and completion of the questionnaires were performed at baseline examination and after completing the training program after three months. The allocation was concealed to all researchers conducting the second examination.

The study was approved by the ethics committee of the Hannover Medical School (Approval No. 3491, 2006). All participants were informed about possible risks and submitted their written consent before inclusion in the study.

4.2. Neurological Examination

4.2.1. EDSS

The disease-specific degree of impairment was assessed using the EDSS, which evaluates the impairment in a variety of functional systems from a comprehensive neurological examination. Participants are scored on a scale ranging from 0 to 10 [33].

4.2.2. Aerobic Capacity/Spiroergometry

Cardiopulmonary exercise testing is a valid method of measuring aerobic capacity in patients with mild to moderate MS [20]. For testing peak oxygen uptake (VO_{2peak}), participants performed an incremental exercise test under supervision of a physician using a spirometric system (Oxycon Delta, CareFusion, Würzburg, Germany) on a speed-independent bicycle ergometer (Ergometrics 900s, Ergoline, Bitz, Germany) with 60 to 70 revolutions per minute, under electrocardiogram (ECG)-monitoring. The incremental test started with a load of 20 W, and the load increased 10 W every minute until the onset of subjective overexertion (peripheral muscle fatigue and/or dyspnoea). The subjective perceived exertion was assessed by the Borg scale ranging from extremely light to extremely hard [34]. The same test protocol was used after the training period.

Maximum oxygen uptake (VO_{2max}) is an important criterion for endurance capacity and describes the maximum volume of oxygen the body can utilize per minute, under maximum load conditions. VO_{2max} is dependent on oxygen exchange, transport, and utilization systems [35]. In fact, VO_{2max} is often achieved only by competitive athletes or highly motivated subjects, and therefore, we have used the term VO_{2peak}. Heart rate and oxygen uptake were continuously measured breath by breath and averaged over 10 s intervals. Blood pressure and blood lactate concentration were acquired at rest, 1 min after the start of testing and every 3 min during the test. Capillary blood samples of 20 µL were taken from the arterialized earlobe, deproteinized and then measured with a lactate analyzer (Ebio 6666, Eppendorf, Berlin, Germany). As a marker of oxidative muscle function, the anaerobic lactate threshold intensity was determined by the method of Roecker *et al.* [36].

The ventilatory anaerobic threshold (VAT) describes the transition from aerobic to partially anaerobic glucose metabolism in muscle. This transition results in increased carbon dioxide exhalation in comparison to oxygen uptake; the increasing build-up of lactate is buffered by bicarbonate and exhaled as carbon dioxide. The VAT represents the lower limit of the aerobic-anaerobic transition zone, is independent of motivation, and is an important parameter for training control. VAT was determined by the v-slope method published by Wassermann [37].

4.3. Isokinetics

Maximum strength was measured in the concentric mode. Isokinetic testing was performed by an experienced sports scientist approximately one hour after spiroergometry. All concentric torque values were done with the CON-TREX Multi-Joint System (CMV AG, Dübendorf, Switzerland) in the concentric/concentric mode. For shoulder and knee tests subjects were seated in an upright position of 85° flexion in the hip joint and 90° flexion in the knee joint. Seat belts were fastened. In order to get maximum stability of the tested lower limb a Velcro strap was fixed to the thigh. Subjects were positioned according to the manufacturer's recommendations. Shoulder tests were performed with the center of rotation of the lever arm in extension to the center of rotation of the knee. This way a boxing-motion was accomplished. The dimension of the arm defined the range of motion. The range of motion for the knee tests was between 90° and 10° flexion. Testing involved a cycle of movements of a body segment at a constant velocity (60° per second), set at the start of each movement. The two antagonist muscle groups were activated alternatively with a loading level set by the patient. We measured the maximum force (F_{max}) of the knee and shoulder extensors and flexors five times for five repetitions, with one-minute breaks between the repetitions. The highest value for each body segment was used for analysis.

4.4. Questionnaires

4.4.1. Short Form-36 Health Survey (SF-36)

The SF-36 represents an established self-assessment method for evaluating Qol, which is widely used in clinical studies [38]. It consists of 36 individual items covering eight subscales of both physical health and mental health. The results are scaled between 0 and 100, with higher values representing a higher subjective Qol.

4.4.2. MFIS (Modified Fatigue Impact Scale)

The MFIS is a shortened version of the Fatigue Impact Scale [39]. This questionnaire examines the impact of fatigue on physical, cognitive and psychosocial health. The score ranges between 0 and 84, where higher scores indicate a greater impairment of the patients. A score of 38 or greater is defined as pathological [40].

4.5. Training Program

The physician-supervised training program lasted three months and consisted of two training sessions per week, each of which was 40 min long and at moderate intensity. Training took place at the Institute of Sports Medicine of the Hannover Medical School. Both the combined training and endurance training programs started with a 20-min workout phase on a bicycle ergometer (Ergometrics 900s, Ergoline, Bitz, Germany) with 60 to 70 revolutions per minute. Heart rate was measured continuously via ECG, whereas blood pressure was measured every 5 min during the first workout phase. To achieve moderate intensity, participants performed at 50% of the maximum workload achieved during the incremental exercise test. At this intensity, all patients trained in the aerobic-anaerobic transition zone (above the VAT and below the anaerobic lactate threshold). Subjective perceived exertion on the Borg scale should be 13 at maximum. During the whole training program, the workload was adjusted according to the heart rate during the first training; the workload was increased by 10% when heart rate and exertion on the Borg scale decreased by a predetermined amount and blood pressure did not exceed 180/100 mmHg.

The second workout phase was performed directly after cycling. The endurance training could be continued on a cross-trainer (Motion Cross 500med; Emotion Fitness, Hochspeyer, Germany), a stepper (Motion Stair 500med; Emotion Fitness, Hochspeyer, Germany), an arm ergometer (Motion Body 500med; Emotion Fitness, Hochspeyer, Germany), a treadmill (Quasar; HP Cosmos, Nussdorf-Traunstein, Germany), a recumbent ergometer (Motion Relax 500med; Emotion Fitness, Hochspeyer, Germany) or a rowing ergometer (Concept2; Indoor Rower, Hamburg, Germany), as preferred by the participant. Heart rate was continuously monitored via ECG. The training heart rate was allowed to be a maximum of 10% above the average heart rate on the bicycle ergometer for all devices except for the recumbent ergometer (same heart rate) and the arm ergometer (heart rate should be approximately 10% lower). The intensity was adjusted according to the heart rate as mentioned above.

The patients in the CWG group underwent a dynamic resistance training program supervised by an experienced sports scientist, so they were able to perform two sets with 10 to 15 repetitions on each machine in a circuit; after completing 15 repetitions two times in a row, the resistance was intensified. As in aerobic training, subjective perceived exertion on the Borg scale should be 13 at maximum. Six out of eight strength machines (Cybex Eagle Line, Medway, MA, USA) could be used to achieve a complex, full-body workout in which multiple muscle groups were trained (leg press, hamstring curl, chest press, row, pull down, overhead press, abdominal, and back extension).

Both training regimes were well tolerated, and there was no worsening of symptoms as a result of the training sessions.

4.6. Statistics

As the main primary analysis, an "intention to treat" analysis was performed with the "last observation carried forward" principle for missing values. To test if this principle was too conservative, a sensitivity "per protocol" analysis was additionally undertaken. If not stated otherwise all shown data are the results of the main analysis.

All data are given as the mean ± standard deviation. Data were tested for a normal distribution using the Kolmogorov–Smirnov test. To establish the possible influence of the training program, analyses of variance with repeated measurements were performed before and after training, including the factor group CWG/EWG. To estimate the effect size, partial eta-squared (η^2) was determined. Thereby, a η^2 of 0.03 represented a power of 75% in the main analysis, 0.05 a power of 93% and 0.10 a power of 99%. For comparing characteristics of the CWG and EWG groups before training, unpaired, two-sided Student's *t*-tests were performed, and Hedges g was calculated as the effect size. Significance was accepted at $p < 0.05$. All tests were performed with SPSS version 22 (IBM Corp., Armonk, NY, USA). Training results were included in the sensitivity analysis if more than 2/3 of the training sessions were attended.

5. Conclusions and Limitations

Regular training for 40 min, two times per week, with moderate intensity increases aerobic capacity and maximum force in patients with low to moderate MS independent of whether endurance or a combined type of training is used. Thus, we conclude that in patients with MS already, 40 min of endurance training are sufficient to improve aerobic capacity. If resistance training is not possible, F_{max} of the extremities can be enhanced when different types of endurance machines which specifically target the upper or lower limb (e.g., rowing, crosstrainer, arm ergometer) are used. Additionally, training improves Qol and reduces fatigue. Referring to the activity guidelines (aerobic training two times a week, for 30 min; strength training two times per week) [8], combined training should be done, preferably, but if not possible, endurance training is a good alternative in patients with mild to moderate MS.

The study was designed as presented above with two intervention groups without a control group, so training-specific effects cannot clearly be differentiated from intervention-bound effects. As the study involved patients whose participation was, in part, self-motivated, the results may not simply be applied to all patients with MS, as it may be assumed that patients interested in sports will show greater capacity and motivation. Improvements in subjective measures, such as Qol, can be explained by social or group effects independent of physical exercise. The patients were randomized as described above, and although there was no statistically significant difference between the two groups, the CWG group had significantly better results in the isokinetic testing of the knee extensors (p = 0.01) and the left flexors (p = 0.02) before starting the training.

High Intensity Exercise in Multiple Sclerosis: Effects on Muscle Contractile Characteristics and Exercise Capacity, a Randomised Controlled Trial

Introduction

Low-to-moderate intensity exercise improves muscle contractile properties and endurance capacity in multiple sclerosis (MS). The impact of high intensity exercise remains unknown.

Methods

Thirty-four MS patients were randomized into a sedentary control group (SED, n = 11) and 2 exercise groups that performed 12 weeks of a high intensity interval ($H_{IT}R$, n = 12) or high intensity continuous cardiovascular training ($H_{CT}R$, n = 11), both in combination with resistance training. M.vastus lateralis fiber cross sectional area (CSA) and proportion, knee-flexor/extensor strength, body composition, maximal endurance capacity and self-reported physical activity levels were assessed before and after 12 weeks.

Results

Compared to SED, 12 weeks of high intensity exercise increased mean fiber CSA ($H_{IT}R$: +21±7%, $H_{CT}R$: +23±5%). Furthermore, fiber type I CSA increased in $H_{CT}R$ (+29±6%), whereas type II (+23±7%) and IIa (+23±6%,) CSA increased in $H_{IT}R$. Muscle strength improved in $H_{IT}R$ and $H_{CT}R$ (between +13±7% and +45±20%) and body fat percentage tended to decrease ($H_{IT}R$: -3.9±2.0% and $H_{CT}R$: -2.5±1.2%). Furthermore, endurance capacity (W_{max} +21±4%, time to exhaustion +24±5%, VO_{2max} +17±5%) and lean tissue mass (+1.4±0.5%) only increased in $H_{IT}R$. Finally self-reported physical activity levels increased 73±19% and 86±27% in $H_{CT}R$ and $H_{IT}R$, respectively.

Conclusion

High intensity cardiovascular exercise combined with resistance training was safe, well tolerated and improved muscle contractile characteristics and endurance capacity in MS.

Trial Registration

ClinicalTrials.gov NCT01845896

Introduction

The heterogeneous symptoms of multiple sclerosis (MS) often lead to a more sedentary lifestyle [1]. This may result in disuse-related loss of exercise capacity and muscle strength, which in turn can affect quality of life [2]. Increasing evidence favors exercise therapy as a method for overall symptom management [3]. Observational [4,5] as well as interventional studies [6–9] have reported improvements in exercise tolerance, muscle strength, functional capacity and health-related quality of life after low-to-moderate intensity cardiovascular or resistance training. Although combined cardiovascular and resistance training could, from a theoretical point of view, positively affect both the cardiovascular system and muscle strength/activation[10], this type of rehabilitation/exercise therapy has not been investigated extensively [11–15].

Several authors already suggested that MS patients could benefit more from higher training intensities [10,16,17], but so far, no studies on combined exercise have evaluated high intensity training in MS. In healthy controls (HC) and in other populations, high intensity exercise and high intensity interval training (H_{IT}) have previously been investigated, showing profound improvements in endurance performance and muscle strength [18,19], reduced subcutaneous and abdominal fat [20], improved functional recovery (after stroke) [21] and beneficial effects to the heart [22], emphasising the need to investigate this in MS.

To date the impact of MS on skeletal muscle characteristics, such as muscle fiber cross sectional area (CSA) and proportion remains unclear. Recently, we reported reduced muscle fiber CSA and changed fiber proportions in MS patients, compared to HC [23]. The impact of exercise on muscle contractile properties in MS has only been investigated by Dalgas and co-workers [24]. They reported increased m.vastus lateralis mean fiber CSA combined with improved muscle strength following 12 weeks of progressive resistance training. Despite the importance of understanding the effects of exercise on muscle fiber characteristics to optimize exercise and rehabilitations programs in MS, the impact of other training modalities and intensities on muscle fiber CSA and fiber type proportion in MS, has not been investigated yet.

To determine the effects of high intensity exercise in MS, this study aimed to investigate the impact of high intensity interval or continuous cardiovascular exercise, both in combination with resistance training, on muscle contractile characteristics, in terms of muscle fiber CSA/proportion, muscle strength and muscle mass and on endurance capacity in MS. It was hypothesized that the applied intense programs could improve mean muscle fiber CSA and proportion as well as muscle strength and endurance capacity.

Methods

Participants

Thirty-four MS patients diagnosed according to McDonald criteria (EDSS range 1–5), aged >18 years, were included following written informed consent (Fig 1). Subjects were excluded if

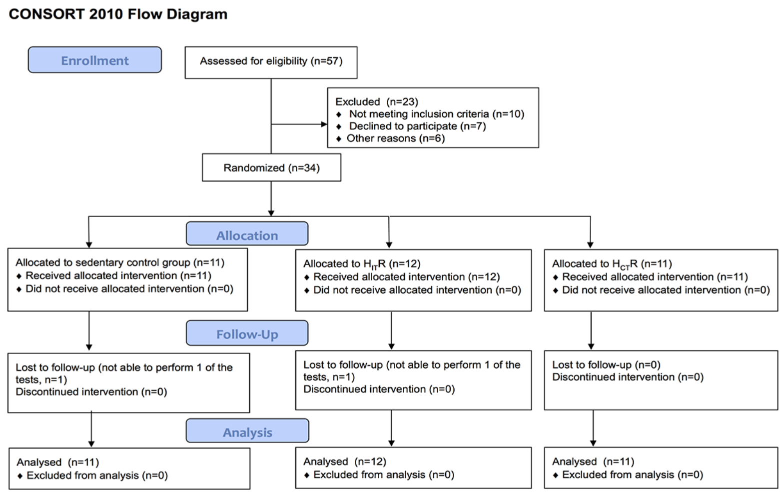

Fig 1. Consort flow diagram for participants' inclusion.

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they had other disorders (cancer, cardiovascular, pulmonary and/or renal), were pregnant, participated in another study, were already physical active, had an acute MS-exacerbation 6 months prior to the start of the study or contra-indications to perform physical exercise.

The study was approved by the ethical committee of Jessa Hospital Hasselt (S1 Protocol) and Hasselt University (12/02/2013), whereupon the preparation of the study started in March 2013 (to order the appropriate equipment, to organise info sessions etc.). Next, this study was registered at ClinicalTrials.gov (NCT01845896, initial release 30/04/2013), at the beginning of patient recruitment (April-June). Furthermore, the authors confirm that all on-going and related trials for this intervention are registered. Finally, all tests were performed in accordance with the Declaration of Helsinki.

Study design overview

All MS patients were randomized, by means of sealed envelopes, into a sedentary control group (SED, n = 11) and 2 exercise groups that performed 12 weeks of a high intensity interval + resistance training ($H_{IT}R$, n = 12) or high intensity continuous endurance + resistance training ($H_{CT}R$, n = 11). M.vastus lateralis fiber CSA and proportion, knee flexor and extensor strength, body composition, maximal endurance capacity and self-reported physical activity levels were assessed before and after the intervention. Neither the patients nor the researchers involved in the project were blinded to group allocation. SED remained physical inactive during the study course and were instructed to continue their current level of physical activity during the period of the study (S1 CONSORT Checklist).

Exercise intervention program

After the baseline measurements, the subjects were enrolled in a well-controlled and supervised training program, to increase cardiorespiratory fitness, as well as strength of the major peripheral muscle groups. Subjects participated in 5 sessions per 2 weeks. Training sessions were interspersed by at least one day of rest, to ensure adequate recovery. Each session started with endurance training, followed by resistance training, interspersed by a short resting period.

$H_{IT}R$ program: Each session started with a 5min warm-up on a cycle ergometer. Hereafter, high intensity cycle interval training was performed. During the first 6 weeks exercise duration gradually increased from 5x1min interspersed by 1min rest intervals to 5x2min and 1min rest

intervals. Exercise intensity was defined as the heart rate, corresponding to 100% of the maximal workload (which was comparable to approximately 80–90% of the maximal heart rate). During the second 6 weeks, duration remained stable at 5x2min and the heart rate increased to reach a level corresponding to 100–120% of the maximal work load (which was comparable to approximately 90–100% of the initial maximal heart rate). The second part consisted of moderate-to-high intensity resistance training (leg press, leg curl, leg extension, vertical traction, arm curl and chest press, Technogym). In order to exercise at similar relative workload, resistance training of the lower limb was performed unilaterally, due to the frequent bilateral strength differences seen between the legs of MS patients.[25] Training intensity and volume were adjusted from 1x10 repetitions to 2x20 repetitions at maximal attainable load. Maximal attainable load was expressed as the maximal load that the subject was able to manage, under guidance and consequent encouragement. By applying the same standardised encouragements in all groups, subjects were stimulated to perform at their personal maximal ability.

$H_{CT}R$ program: Each session started with a cardiovascular part, consisting of cycling and treadmill walking/running (Technogym). Session duration and exercise intensity increased as the intervention progressed, starting from 1x6min/session to 2x10min/session, at a high workload, corresponding to 80–90% of maximal heart rate and according to individual capabilities. The second part of the training session comprised similar resistance training, as described in the $H_{IT}R$ program.

All exercises were performed at a high workload corresponding to 14–16 ratings of perceived exertion on 20-point Borg scale (RPE) and were adjusted to individual disability level. The Borg Rating of Perceiver Exertion Scale measures perceived exertion and is used to document the person's exertion during a test or to assess the intensity of training and rehabilitation. The scale ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion". Continuous encouragement by the instructors led to a systematic increase of the training load over the 12-week training period. All sessions were ended by stretching of the extremities, and RPE-level was recorded.

Primary outcome measure

1. Muscle fiber CSA and proportion. To investigate muscle fiber CSA and proportion, muscle biopsies form the middle part of the m.vastus lateralis (Bergström needle technique) of the weakest leg (see isometric muscle strength measurements) were collected by an experienced medical doctor. The second biopsy, following 12 weeks of exercise or usual care, was taken 2-3cm proximal to the biopsy taken at baseline. Muscle samples were immediately mounted with Tissue-Tek, frozen in isopentane cooled with liquid nitrogen and stored at -80°C, until further analysis. The cross-sections of the biopsies, collected at baseline and after 12 weeks, were processed simultaneously.

Serial transverse sections (9μm) from the obtained muscle samples were cut at -20°C and stained by means of ATPase histochemistry, after preincubation at pH 4.4, 4.6 and 10.3, essentially following the procedure of Brooke and Kaiser [26]. The serial sections were visualized and analyzed using a Leica DM2000 microscope (Leica, Stockholm, Sweden) and a Leica Hi-resolution Color DFC camera (Leica, Stockholm, Sweden) combined with image-analysis software (Leica Qwin ver. 3, Leica, Stockholm, Sweden). A fiber mask of the stained sections was drawn automatically and afterwards this mask was fitted manually to the cell borders of the selected fibers. Only fibers cut perpendicularly to their longitudinal axis were used for the determination of fiber size. On average 170±10 fibers were calculated and included in the CSA and fiber type analyses.

Calculation of the fiber CSA was performed for the major fiber types (I, IIa and IIx) and for the mean fiber CSA, since the number of type IIax and IIc fibers was too small for statistical comparison and CSA calculation.

Secondary outcome measures

Approximately 1–2 weeks before the muscle biopsy was performed secondary outcome measures were assessed from all subjects.

1. Isometric muscle strength. After 5min of warming-up on a cycle ergometer and following habitation, the maximal voluntary isometric muscle strength of the knee extensors and flexors (45° and 90° knee angle) were measured, as described elsewhere [27], using an isokinetic dynamometer (System 3, Biodex, ENRAF-NONIUS, New York, USA). Two maximal isometric extensions (4s) and flexions (4s), followed by a 30s rest interval, were performed. The highest isometric extension and flexion peak torques (Nm) were selected as the maximal isometric strength. Baseline results were used to classify the legs of each patient as weakest or strongest leg. This subdivision was maintained in further analysis, replacing a conventional left-right classification.

2. Endurance capacity. During the exercise test to volitional fatigue, an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany) with pulmonary gas exchange analysis (Jaeger Oxycon, Erich Jaeger GmbH, Germany) was used (cycling frequency: 70 rpm). Jaeger calibration (ambient conditions, volume calibration and O_2/CO_2 calibration) was performed at the start of each test day. This test was performed at least 48 hours separated from the isometric muscle strength test to exclude interference of muscle fatigue. Female and male MS patients started at 20W and 30W, respectively, during the first minute. Hereafter, workloads increased, respectively, 10W and 15W per minute. Oxygen uptake (VO_2), expiratory volume (VE), and respiratory exchange ratio (RER) were collected breath-by-breath and averaged every 10 seconds. Using a 12-lead ECG device, heart rate (HR) was monitored every minute. At the end of the test RER values were evaluated to verify that the test was maximal ($RER \geq 1.15$) [28]. In addition, maximal cycling resistance (W_{max}), maximal heart rate (HR_{max}), test duration and VO_{2max}, defined as the corresponding load, heart rate, amount of minutes and oxygen uptake measured at the level of exhaustion, were reported.

3. Body composition. A Dual Energy X-ray Absorptiometry scan (Hologic Series Delphi-A Fan Beam X-ray Bone Densitometer, Vilvoorde, Belgium) was performed pre- en post-intervention. Fat and lean tissue mass were obtained for whole body, legs, trunk, gynoid and android region. Waist-to-hip fat mass ratio (android fat (g)/gynoid fat (g) ratio) and fat mass of the trunk/fat mass of the limbs ratio were calculated.

4. Physical activity level. Before and after the intervention, patients were asked to report their physical activity level by using the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) [29]. Respondents were asked to report the number of days and average hours in a day spent engaging in 13 activities (including recreational, household, and occupational activities) over the last 7 days. Frequency responses range from 1 (never) to 4 (often), and duration responses range from 1 (less than 1 hour) to 4 (more than 4 hours). Total scores were calculated as the product of the average hours spent in an activity daily and the metabolic equivalents (MET) summed over each item. Scores range from 0 (no activity) to over 100 MET*h/week (very high). At baseline all patients needed to be physical inactive, to be included in the study. Physical inactivity was defined as < 30 MET*h/week.

Statistical analysis

All data were analyzed using SAS 9.2 software (SAS Institute Inc, Cary, USA). First normality was checked using the Shapiro-Wilk test for all variables. Differences between MS groups

Table 1. Baseline subject and disease characteristics. Data is presented as mean ± SE. Differences between groups (SED, $H_{CT}R$ and $H_{IT}R$) were analysed by a one-way ANOVA. Abbreviations used: MS, multiple sclerosis; SED, sedentary group; $H_{CT}R$, intense continuous endurance + resistance training; $H_{IT}R$, high intensity interval training + resistance training, BMI, body mass index; RR, relapsing remitting; CP, chronic progressive; EDSS, expanded disability status scale; immunomodulatory: interferon β, glatiramer acetate, fingolimod, natalizumab.

	SED (n = 11)	$H_{CT}R$ (n = 11)	$H_{IT}R$ (n = 12)	p-value
age (y)	47±3	47±3	43±3	0.22
height (m)	1.67±0.02	1.69±0.02	1.7±0.02	0.32
weight (kg)	75.8±3.6	70.2±3.7	75.9±4.1	0.17
BMI (kg/m^2)	27.0±1.4	24.4±1.2	26.1±1.14	0.11
Lean tissue mass (kg)	43.2±2.1	45.4±2.6	48.5±3.1	0.11
Fat percentage (%)	38.2±2.1	33.6±2.8	36.2±1.9	0.20
gender (m/f)	2/9	5/6	5/7	0.12
type MS (RR/CP)	8/3	8/3	10/2	0.8
EDSS	2.5±0.3	2.7±0.3	2.3±0.3	0.41
Immunomodulatory MS treatment	72%	80%	80%	0.23

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(SED, $H_{CT}R$ and $H_{IT}R$) were analysed by a one-way ANOVA, whereas within group differences (post minus pre) were analysed with a paired student's t-test. Relative changes due to the intervention were calculated as the mean of the individual changes and expressed as a percentage. Correlations between changes of the primary and changes of the secondary outcome measures on grouped data from all groups were analysed by means of Pearson's correlation analysis. Multiple comparison was corrected by means of Bonferroni correction. All data are presented as mean±SE. $P<0.01$ represents the threshold for statistical significance.

Results

Baseline subject characteristics and adherence to the intervention

At baseline, no differences in general subject and disease characteristics (Table 1) as well as outcome measures were found between groups. Approximately 90% of the 30 supervised training sessions were attended in both exercise groups and no severe symptoms exacerbations and/or adverse events were reported. Furthermore, no patient drop out was noted.

Primary outcome measure

1. Muscle fiber CSA and proportion. Fig 2 shows a representative image of muscle fiber types before and after high intensity exercise. In SED muscle fiber CSA and proportion did not change ($p>0.05$). Mean CSA significantly increased in $H_{IT}R$ and $H_{CT}R$ following 12 weeks of exercise (p = 0.009 and p = 0.002, respectively). Furthermore, muscle fiber type I CSA increased in $H_{CT}R$ (p = 0.003), whereas muscle fiber type II and IIa increased in $H_{IT}R$ (p = 0.007 and p = 0.002, respectively). Fiber type IIx CSA did not change ($p>0.05$). In general, no changes in fiber type proportion were observed in any exercise group after 12 weeks of exercise. However, within group effects were observed on type IIx of $H_{CT}R$ (p = 0.001), after comparison of the pre- and post-intervention fiber type proportion values (Table 2).

Secondary outcome measures

1. Isometric muscle strength. Muscle strength of SED remained stable during 12 weeks of usual care ($p>0.05$, Fig 3). Compared to SED, knee flexion and knee extension strength of the weakest leg of $H_{IT}R$ improved by 24±13 to 44±20% (p values between 0.01 and 0.006), whereas only hamstring strength of the strongest leg of $H_{IT}R$ improved by 13±7 to 20±7% (p = 0.006).

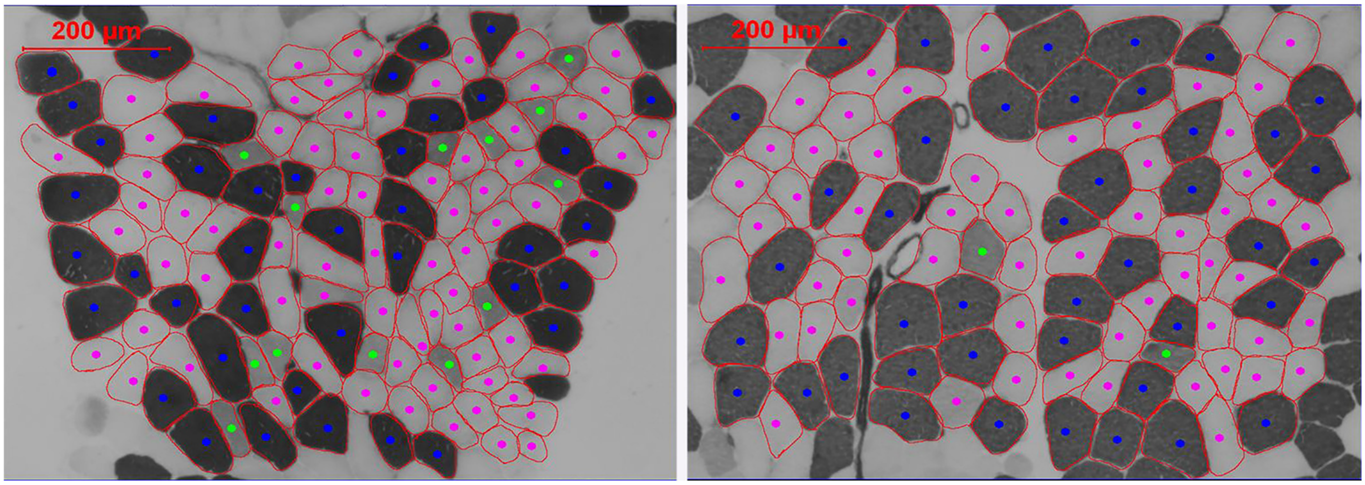

Fig 2. Representative image of fiber type analysis before (left) and after (right) high intensity exercise. Different fiber types are distinguished by color (dark blue: type I, pink: type IIa, green: type IIx, light blue: type IIc). Calculation of the fiber CSA was performed for the major fiber types (I, IIa and IIx) and for the mean fiber CSA, since the number of fibers expressing the minor fiber types (IIax and IIc) was too small for statistical comparison and CSA calculation.

Furthermore, $H_{CT}R$ flexion and extension strength improved, from pre- to post trial, in the weakest leg by 19±9 to 33±17% (p values between 0.01 and 0.006), whereas muscle strength of the strongest leg remained stable (p>0.05).

2. Endurance capacity. After 12 weeks, endurance capacity variables remained stable in SED and $H_{CT}R$. Compared to SED and $H_{CT}R$, W_{max} (+21±4%, p = 0.0001), test duration (+24 ±5%, p = 0.00008) and VO_{2max} (+17±5%, p = 0.001) significantly improved in $H_{IT}R$ (Table 3).

Table 2. Muscle fiber type proportion and cross sectional area (CSA) at baseline and after 12 weeks of usual care or high intensity aerobic exercise in combination with resistance training. Data are reported as mean ± SE. Differences between groups (SED, $H_{CT}R$ and $H_{IT}R$) were analysed by a one-way ANOVA, whereas within group differences (post minus pre) were analysed with a paired student's t-test. Relative changes due to the intervention were calculated as the mean of the individual changes and expressed as a percentage. Abbreviations used: SED, sedentary (usual care); $H_{CT}R$, high intensity continuous exercise + resistance training; $H_{IT}R$, high intensity interval training + resistance training.

	SED			$H_{CT}R$			$H_{IT}R$		
	Pre	Post	%	Pre	Post	%	Pre	Post	%
Fiber type proportion (%)									
Type I	44.2 ± 3.9	47.5 ± 2.9	**7.9 ± 7.5**	40.1 ± 4.7	46.9 ± 4.7[b]	**26.8 ± 11.3**	41.3 ± 3.0	46.3 ± 2.6[b]	**21.7 ± 10.1**
Type IIa	34.2 ± 3.9	34.2 ± 2.3	**5.1 ± 13.1**	34.1 ± 2.9	38.9 ± 4.6	**6.6 ± 7.5**	40.9 ± 3.8	44.5 ± 2.4	**6.9 ± 8.1**
Type IIx	21.2 ± 4.5	17.7 ± 2.0	**19.2 ± 12.6**	24.3 ± 2.7	13.5 ± 2.6[a]	**-46.0 ± 7.6**[c]	18.5 ± 2.8	10.1 ± 2.8	**-20.1 ± 25.4**
Fiber CSA (μm^2)									
Mean	3738 ± 267	3740 ± 431	**3.5 ± 4.3**	3551 ± 351	3905 ± 408[a]	**23.3 ± 4.9**[c]	4038 ± 321	4892 ±379[a]	**21.1 ± 7.3**[d]
Type I	4078 ± 384	4050 ± 531	**4.0 ± 5.5**	3630 ± 443	4071 ± 470[a]	**29.8 ± 5.5**[c]	4410 ± 188	4916 ± 399	**12.1 ± 8.7**
Type II	3487 ± 265	3478 ± 334	**6.9 ± 5.8**	3285 ± 321	3622 ± 398[b]	**20.8 ± 7.9**	3612 ± 429	4551 ± 462[a]	**22.7 ± 6.8**
Type IIa	3703 ± 306	3729 ± 402	**3.6 ± 3.1**	3719 ± 366	4014 ± 522[b]	**15.1 ± 5.3**	4037 ± 444	5034 ± 447[a]	**22.8 ± 6.2**[d]
Type IIx	3446 ± 305	3191 ± 318	**5.4 ± 8.2**	2771 ± 277	2955 ± 258	**14.5 ± 8.9**	3187 ± 438	3920 ± 519[b]	**23.6 ± 8.8**

[a] p<0.01

[b] p ≤ 0.05, compared with pre-intervention value, within group.

[c] p<0.01

[d] p ≤ 0.05, pre to post change compared with change from pre to post in SED.

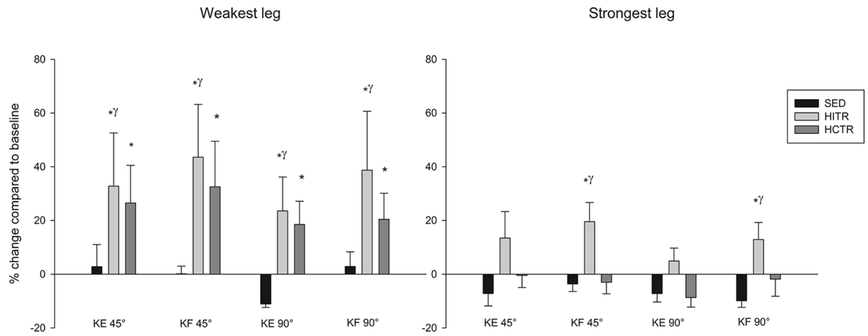

Fig 3. Percentage change of knee extension and flexion after 12 weeks of physical inactive living (usual care, SED), high intensity continuous training + resistance training ($H_{CT}R$) and high intensity interval training + resistance training ($H_{IT}R$). Data are reported as mean ± SE. * p<0.05, compared with pre-intervention value, within group. ˠ p<0.05, pre to post change compared with change from pre to post in SED. Abbreviations used: KF, knee flexion; KE, knee extension.

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3. Body composition. Following 12 weeks of exercise, body weight remained stable in all groups (p>0.05). Within $H_{IT}R$ and $H_{CT}R$, body fat percentage tended to decrease by 3.9±2.0% (p = 0.04) and 2.5±1.2% (p = 0.02), respectively. Furthermore, lean tissue mass significantly increased 1.4±0.5% within $H_{IT}R$ (p = 0.01), whereas it remained stable in $H_{CT}R$ and SED

Table 3. Exercise capacity, body composition and physical activity level after 12 weeks of usual care or high intensity aerobic exercise in combination with resistance training. Data are reported as mean ± SE. Differences between groups (SED, $H_{CT}R$ and $H_{IT}R$) were analysed by a one-way ANOVA, whereas within group differences (post minus pre) were analysed with a paired student's t-test. Relative changes due to the intervention were calculated as the mean of the individual changes and expressed as a percentage. Abbreviations used: SED, sedentary (usual care); $H_{CT}R$, high intensity continuous exercise + resistance training; $H_{IT}R$, high intensity interval training + resistance training; MET, metabolic equivalent.

	SED			$H_{CT}R$			$H_{IT}R$		
	Pre	Post	%	Pre	Post	%	Pre	Post	%
Exercise capacity:									
Maximal cycling resistance (watt)	121±8	115±11	**-4.6±2.7**	131±18	133±18	**3.6±2.8**	158±15	188±15[a]	**21.2±3.9**[c]
Maximal cycling resistance (watt/kg)	1.6±0.12	1.6±0.15	**-4.6±2.7**	1.85±0.24	1.9±0.23	**3.6±2.8**	2.0±0.17	2.4±0.16[a]	**21.2±3.9**[c]
Test duration (min)	10.4±0.8	9.9±0.8	**-3.1±2.9**	9.5±1.0	9.8±0.9	**5.2±3.1**	12.1±0.9	14.5±0.9[a]	**24.7±4.6**[c]
VO_2 max (ml/min)	1647±133	1645±160	**2.5±4.1**	1870±238	1969±230	**7.5±5.8**	2031±186	2379±197[a]	**17.8±4.6**[c]
VO_2 max (ml/min/kg)	21.9±1.8	23.6±2.1	**2.5±4.1**	26.3±3.1	28.2±3.0	**7.5±5.8**	26.6±2.2	30.7±2.1[a]	**17.8±4.6**[c]
Minute Ventilation (l/min)	57±4	62±7	**9.9±6.5**	70±11	76±11[b]	**13.3±7.7**	76±7	96±6[a]	**32.7±8.7**
Breathing frequency	32±2	39±3[a]	**25.7±5.5**	32±2	37±2[a]	**14.3±4.6**	32±2	41±3[a]	**39.6±16.8**
Tidal Volume (ml)	1789±138	1617±154	**-11.2±6.2**	2155±241	2086±287	**-1.2±4.6**	2394±190	2425±189	**-0.5±5.2**
RER max	1.18±0.04	1.17±0.03	**-3.2±2.8**	1.3±0.03	1.2±0.02	**-2.2±2.9**	1.2±0.03	1.2±0.02	**1.3±2.5**
HR rest (beats/min)	75±4	87±4[a]	**14.3±3.8**	76±3	80±4	**7.0±5.8**	75±3	84±3	**12.5±4.6**
HR max (beats/min)	142±7	153±5	**6.5±2.3**	154±6	162±6[b]	**3.7±1.5**	160±6	168±5[a]	**6.2±2.2**
Body composition:									
Lean tissue mass (kg)	43.2±2.1	43.5±2.1	**0.6±0.6**	45.4±2.6	46.2±2.5	**0.9±0.9**	48.5±3.1	49.9±3.1[a]	**1.4±0.5**
Fat percentage (%)	38.2±2.1	37.3±2.2	**-2.8±1.6**	33.6±2.8	32.6±2.8[b]	**-2.5±1.2**	36.2±1.9	34.3±2.0[b]	**-3.9±2.0**
Physical activity level: (MET*h/week)	16±2.6	15.8±3.7	**2.9±13**	14.7±2.7	23.9±4.4[a]	**73±19**[c]	25.8±6.6	37.6±7.2[a]	**86±27**[c]

a p<0.01,

b p<0.05, compared with pre-intervention value, within group.

c p<0.01, pre to post change compared with change from pre to post in SED.

($p>0.05$, Table 3). Finally, other adipose and lean tissue mass indices remained stable in all groups ($p>0.05$).

4. Physical activity level. Compared to SED, the physical activity level of $H_{IT}R$ and $H_{CT}R$ significantly increased by 86±27% (p = 0.004) and 73±19% (p = 0.003), respectively, following 12 weeks of exercise. In SED the physical activity level remained stable (Table 3).

Correlations

Overall, no significant correlations were found between the change of the primary and secondary outcome measures on pooled data.

Discussion

This study is the first to investigate the impact of high intensity cardiovascular exercise combined with resistance training on muscle contractile characteristics and endurance capacity in MS. Moreover, 12 weeks of the applied high intensity programs were safe, well tolerated and induced beneficial adaptations in MS patients. In particular, muscle fiber CSA, muscle strength of the weaker legs and self-reported physical activity levels improved following both $H_{IT}R$ and $H_{CT}R$. In addition, further improvements of the endurance capacity, muscle flexion strength of the stronger legs and lean tissue mass were only seen in $H_{IT}R$. These results are clinically relevant, due to the need for exercise programs that are able to counteract reduced endurance capacity, muscle strength and muscle mass of particularly the lower limbs, enhancing physical function in MS patients.

Safety and tolerability

Several studies have already demonstrated the benefits of resistance training [6] or endurance training [7–9] in MS. The effect of combined training has only been sparsely explored [11–14] and the impact of high intensity combined exercise has never been investigated before. The latter could be explained by safety concerns regarding the symptom instability of MS patients often seen during/after high intensity exercise, which is frequently caused by the exercise-induced increase in body temperature [30]. Interestingly, no dropout or adverse events were reported during and after 12 weeks of $H_{IT}R$ and $H_{CT}R$, demonstrating that mild-to-moderately impaired MS patients tolerate intense exercise programs.

Continuous vs. interval training

The present study showed an improvement of the endurance capacity, muscle flexion strength of the stronger legs and lean tissue mass in $H_{IT}R$, and improved muscle strength of the weaker leg and self-reported physical activity levels in $H_{IT}R$ and $H_{CT}R$, suggesting that exercise efficiency is even higher in $H_{IT}R$. This is in line with literature in other patient populations, investigating the difference between continue and interval training, stating that exercise intensity is an important factor to improve, amongst others, cardiorespiratory fitness [31–33], but also arterial stiffness [34] and hypertension [35]. In general, the magnitude of improvements was greater after high intensity interval training. Importantly, and as already suggested by others [10], the observed training improvements in the present study were often larger compared to those reported after mild-to-moderate combined exercise programs in MS patients [11–15]. This suggests that higher training intensities are more effective and that training adaptations are intensity related in MS.

Interestingly, the maximal heart rate changed from baseline to post training in $H_{IT}R$. This can possibly be explained due to the fact that these patients might have impaired chronotropic regulation at baseline, which can broadly be defined as the inability of the heart to increase its rate commensurate with increased activity or demand, which might be induced by cardiac autonomic dysfunction, as already reported by our research group [36,37]. In other populations, exercise is able to increase peak heart rate and to reverse, at least partially, impaired chronotropic regulation [38–42], which contribute to the exercise-induced increase in exercise capacity and other outcome measures. Since this was only seen in $H_{IT}R$ and not in $H_{CT}R$, it suggests again that higher training intensities might be more effective in MS. Nevertheless, impaired chronotropic regulation was never investigated into depth in MS patients and warrants further research in the future.

Muscular effects

Recently, we reported that MS affects muscle fiber CSA and proportion [23]. To our knowledge, only Dalgas et al. investigated the effects of exercise (progressive resistance training) on muscle fiber CSA in MS [24], reporting increased mean muscle fiber CSA (8±15%), predominantly in type II muscle fiber CSA (14±19%) and a tendency towards increased type I CSA [24]. In the present study, mean muscle fiber CSA ($H_{IT}R$: 21±7%, $H_{CT}R$: 23±5%) and lean muscle mass further increased, suggesting an additional value of the high intensity aerobic exercise. This is, partly, in accordance with results reported in sedentary HC, demonstrating a significant increase of the area of type I and IIx fibers after high intensity interval training [43]. In addition, high intensity aerobic exercise induced an increased CSA of both type IIa and IIx fibers and no changes in type I fiber size in elite ice hockey players [44].

Based on an often more inactive lifestyle of MS patients, Dalgas et al. expected an inactivity-related higher proportion of type IIx fibers and a possibility to transform type IIx to IIa fibers after progressive resistance training [45,46]. However, they were not able to report any changes in the proportion of fiber types. In the present study, type IIx proportions decreased after 12 weeks of $H_{CT}R$, whereas the type I proportion tended to increase in $H_{CT}R$ and $H_{IT}R$. These results are comparable with data reported in healthy elderly populations, reporting a reduction of the type IIx proportion and an increase of the proportion of the type IIa fibers [47,48]. Interestingly, these studies used higher training frequencies [47] or longer training periods [48], compared to the work of Dalgas et al. [24], suggesting that a higher training volume and intensity is required to induce fiber type changes than to induce changes in fiber type CSA.

Limitations

Since this is the first study that investigated the effects of high intensity exercise on muscle fiber CSA and proportion in MS, we were not able to perform a pre-trial power analysis, due to the absence of a defined effect size. Nevertheless, a post-hoc power analysis (R 2.15.2 software) on mean muscle fiber CSA and based on the present results, demonstrated that 5 persons in each group would be sufficient to provide a >80% power to detect a 20% increase of mean muscle fiber CSA after 12 weeks of high intensity exercise ($p = 0.05$, $\sigma = 7\%$), demonstrating a suitable sample size in the present study. Secondly, given the ethical concerns we collected only one biopsy per test, despite the recommendation of Lexell et al. [49] to optimally collect three biopsies from different depths of the muscle and to analyse >150 fibers from each sample to reduce sampling error. Furthermore, since self-reported physical activity measures are not perfect measures, we propose the use of accelerometers in future studies. Also the inclusion of a follow up examination, to determine whether the improvements are long lasting, could be recommended in future studies. Finally, given the nature of the design, social interactions between MS patients could possibly influence intervention outcomes.

Conclusion

The present study showed that 12 weeks of high intensity cardiovascular exercise in combination with resistance training was safe, well tolerated and improved muscle contractile characteristics and endurance capacity, with interval training seemingly superior to continuous training.