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Ventilatory function during exercise in multiple sclerosis and impact of training intervention: cross-sectional and randomized controlled trial

Dominique Hansen, PhD[1,2]; Inez Wens, MSc[1]; Charly Keytsman, MSc[1]; Kenneth Verboven, MSc[1]; Paul Dendale, MD, PhD[1,2]; Bert O Eijnde, PhD[1]

[1]REVAL – Rehabilitation Research Center, BIOMED- Biomedical Research Center, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium

[2]Jessa Hospital, Heart Centre Hasselt, Hasselt, Belgium

Short title: Ventilatory dysfunction during exercise in MS

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Address correspondence:

Dominique Hansen, PhD

Hasselt University, Faculty of Medicine and Life Sciences

Agoralaan, Building A, 3590 Diepenbeek, Belgium

Dominique.hansen@uhasselt.be

Tel 0032 (0)11 294978

Fax 0032 (0)11 269329

Abstract

Background

Patients with MS (pwMS) often experience resting ventilatory anomalies. Ventilatory function during exercise and impact of long-term training intervention remains however uncertain.

Aim

To examine the ventilatory function during exercise and impact of a 6-month training intervention in pwMS.

Design

Combination of a cross-sectional (part 1) and randomized controlled trial (part 2).

Setting

University rehabilitation facility.

Population

Caucasian patients with MS and healthy controls.

Methods

In part 1, the ventilatory function during submaximal endurance exercise was compared between pwMS (n=37) and healthy participants (n=15). In part 2, pwMS were then randomly assigned to a 6-month training intervention (n=16) or usual care (n=11). Following training intervention, ventilatory function during exercise was re-evaluated.

Results

Despite comparable relative exercise testing intensities between groups in part 1, significantly elevated steady-state exercise dead space/tidal volume ratio, O_2 uptake and CO_2 output equivalent, end-tidal O_2 pressure, ratings of perceived exertion and lowered end-tidal CO_2 pressure and O_2 pulse was observed in pwMS ($p<0.05$). The degree of ventilatory dysfunction during exercise correlated significantly with ratings of perceived exertion and blood lactate content ($p<0.05$). In part 2, despite an improved exercise tolerance (based on reductions in heart rate, blood lactate content and ratings of perceived exertion during exercise at similar workload) after a 6-month training intervention, ventilatory dysfunction remained present during endurance exercise ($p>0.05$).

Conclusion

Patients with MS experience a ventilatory dysfunction during endurance exercise, which is related to worse exercise tolerance. This ventilatory anomaly remains present after long-term training intervention.

Clinical rehabilitation impact

Patients with MS experience ventilatory dysfunction during exercise. This dysfunction is related to exercise tolerance and ratings of perceived exertion. Long-term exercise training did not remediate this ventilatory dysfunction. The systematic examination of the pulmonary/cardiovascular system at rest and during exercise is recommended in MS.

Keywords: multiple sclerosis, exercise, pulmonary function, gas exchange, ventilation, rehabilitation

Introduction

In clinical practice lung function anomalies are often overlooked or not closely evaluated in patients with MS (pwMS) until severe lung complications emerge.[1] However, pulmonary function is impaired in many pwMS, which is typically characterized by a reduced pulmonary muscle strength and/or diffusion capacity.[2,3]

Given the elevated likelihood for the development of pulmonary dysfunction in MS, it is important to understand the ventilatory function during exercise. Even though the aetiology of exercise intolerance in pwMS remains under intense debate[4-7] this might, at least in part, be related to ventilatory dysfunction during exercise. For example, in patients with chronic lung disease or heart failure exercise tolerance is impaired by ventilatory anomalies.[8,9] Moreover, in pwMS significant relations are present between resting pulmonary function and exercise tolerance.[10] To unravel the aetiology of exercise intolerance in MS, it is mandatory to understand/explore the ventilatory physiology during exercise in MS and the relations with exercise tolerance.

However, ventilatory function during exercise remains incompletely understood in MS. Previous studies reported elevated carbon dioxide (VE/VCO_2) equivalents during submaximal exercise and elevated dead space ventilation (Vd/Vt ratios) during peak exercise in pwMS.[11-13] In these studies elicited exercise intensities and/or subject characteristics were significantly different between pwMS and healthy controls[11,12] or few ventilatory parameters were assessed.[13] Ventilatory function during exercise in pwMS therefore deserves further examination.

Patients with MS are included in rehabilitation programs to improve and/or treat multiple health parameters and/or symptoms. However, the impact of long-term endurance and/or resistance training on ventilatory function during exercise in pwMS is unknown. In other patient populations, such as in chronic obstructive pulmonary disease and heart failure, significant improvements in pulmonary function during submaximal exercise have been observed when following an endurance exercise training intervention.[14,15] Moreover, these improvements in pulmonary function during exercise correlated with advances in exercise tolerance. To further explore the clinical benefits of

exercise intervention in MS, and understand how improvements in exercise capacity emerge, it should be studied whether exercise training effectively remediates ventilatory dysfunction during exercise in MS, when present.

The aim of this study was to examine ventilatory function during endurance exercise in pwMS vs. healthy controls, and the impact of a long-term training intervention on ventilatory function during exercise in pwMS. We hypothesized that a ventilatory dysfunction during exercise is present in pwMS and that this is remediated by training intervention.

Materials and methods

Design

This was a combination of a cross-sectional study (part 1) and randomized controlled trial (part 2) at Hasselt University, Belgium. In part 1, following EDSS[16] and MS type determination, screening of medication intake, assessment of body mass index and physical activity, ventilatory function during submaximal endurance exercise was assessed in pwMS and healthy subjects. In part 2 pwMS were randomly assigned to six months of exercise training or control follow-up after a baseline exercise test, and ventilatory function during exercise was re-evaluated after this timeframe (Figure 1). In part 2 assessors were blinded for treatment allocation but therapists could not be blinded for treatment allocation. Both studies were conducted in accordance with the amended Declaration of Helsinki. The ethical committee of Hasselt University approved the protocol and written informed consent was obtained from all participants.

Setting and participants

This study was conducted in an university rehabilitation facility. From March 2011 to August 2011 37 pwMS (EDSS 0.5-6.0) and 15 healthy controls participated in part 1 after local advertisement, and 36 pwMS further participated in part 2 after personal approach. All participants were of Caucasian origin and lived in Belgium. In part 1, pwMS and healthy subjects were primarily matched for age, gender

and body mass index. In part 2, groups were primarily matched for age, gender and EDSS. All participants were sedentary (<2h sports activities/week), aged 18-75 yrs, and pwMS had been diagnosed for at least 12 months by a neurologist according to the McDonald criteria. None of the participants were diagnosed with cardiovascular, renal or pulmonary disease. Sample size of part 1 was based on a previous study observing significant ventilatory anomalies during exercise in pwMS with sufficient statistical power (α>0.80, based on peak exercise Vd/Vt ratio, n=10 pwMS vs. n=10 healthy controls in this study).[13] For part 2 no data are available to estimate the impact of training intervention on ventilatory function during exercise in pwMS. Therefore, we selected a sufficient sample to be able to observe significant positive effects of exercise training on exercise tolerance (α>0.8, based on VO_{2peak}, n=11 pwMS in this study).[17]

Randomization and intervention

In part 2, pwMS were randomly assigned to an intervention (n=23) or control group (n=13) in a 2:1 (intervention:control) ratio by one of the therapists by sealed envelope. Due to drop-out during follow-up, data from 16 vs 11 pwMS were analyzed at the end of study. Participants of the intervention group followed a supervised 6-month combined endurance-resistance training program (five sessions/two weeks). The training sessions were executed between 8-12 AM. Endurance exercises were executed first, followed by resistance exercises (three upper body and three lower body exercises). Exercise workload (at 12-14 RPE on 20-point scale) and session duration (1x6→3x10min/session during endurance training (walking and cycling), 1x10rep→4x15rep during resistance training) gradually increased during intervention. Exercise volume and duration were increased according to individual capabilities. During the entire training period, participants were strongly encouraged and supervised by instructors to increase exercise volume and/or training load in the following session if they felt competent of performing more than the prescribed load or volume. These incentives led to a systematic increase in training load and volume over the 24-week training period but with low probability for medical complications. After each exercise session, the

training load was noted and participants were asked if they had experienced any difficulties during exercise. All participants completed at least 54 out of 60 training sessions. Participants from the control group did not follow a structured exercise intervention and were advised to maintain current daily physical activity level.

Outcomes and follow-up

Primary outcome measurements were indicators of ventilatory function during exercise: oxygen uptake (VO_2, ml/min), carbon dioxide output (VCO_2, ml/min), expiratory volume (VE, l/min), respiratory rate (RR), expiratory tidal volume (Vt, l/min), dead space/tidal volume ratio (Vd/Vt, %), oxygen uptake (VE/VO_2) and carbon dioxide output equivalent (VE/VCO_2), end-tidal oxygen ($PETO_2$, KPa) and carbon dioxide pressure ($PETCO_2$, KPa), oxygen pulse (VO_2/HR). We decided to collect data from a large amount of pulmonary parameters to be better able to elucidate the pathophysiology and clinical consequences of pulmonary dysfunction during exercise in MS. The VO_2 and VCO_2 reflect the total amount of oxygen uptake and carbon dioxide output, respectively, while VE specifies total ventilatory air movement. $PETO_2$ and $PETCO_2$ are used to estimate partial arterial O_2 and CO_2 pressures, respectively. VE/VO_2 and VE/VCO_2 reflect the efficiency for oxygen uptake and carbon dioxide output at the level of the lungs, respectively. Vd/Vt is a parameter used to assess alveolar and dead space ventilation ratio and ventilation-perfusion match. VO_2/HR indicates cardiac stroke volume. Secondary outcome measurements were heart rate, ratings of perceived exertion (RPE) on a 20-point Borg scale, and blood lactate content during exercise testing.

Body mass index: from body weight and length assessment, body mass index (BMI) was calculated.

Daily physical activity: the metabolic equivalent (MET) * hours/week was calculated from the 13-item Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) questionnaire.[18]

Exercise tolerance: participants performed a 6-min constant-workload exercise test on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Germany) with continuously breath-by-breath measured pulmonary gas exchange (mass spectrometer and volume

turbine system, Jaeger Oxycon, Erich Jaeger GmbH, Germany). All participants completed the entire exercise test. Participants were advised not to perform any exercise 24 hours before testing, and only eat a light meal at least two hours prior to testing. Participants were seated on bike for three minutes to obtain resting data. Next, participants cycled at 70 rpm against a resistance corresponding to 25% (pwMS) or 35% (healthy participants) of predicted maximal cycling power output (W_{max}).[4] Predicted W_{max} was calculated by previously published formulae.[19] In part 1, a higher cycling resistance was selected for healthy participants, as opposed to pwMS, because a higher exercise capacity was anticipated in the former, while relative exercise intensities should be equal between groups to be able to compare ventilatory parameters. In a previous study, the selection of these exercise intensities within these groups led to a comparable blood lactate content and heart rate between groups.[4] VO_2, VCO_2, VE, RR, Vt, Vd/Vt ratio, VE/VO_2, VE/VCO_2, $PETO_2$, $PETCO_2$, and VO_2/HR were assessed breath-by-breath and averaged every 10 seconds. Heart rate (HR, beats/min) was monitored by 12-lead ECG device. Throughout this manuscript ventilatory parameters and HR during steady-state exercise (averaged outcome during final minute of exercise) will be mentioned. Predicted maximal HR was calculated by 220–age. During the final minute of exercise a capillary blood sample was obtained from the fingertip to analyze blood lactate concentrations (Accutrend Plus, Roche Diagnostics Limited, UK) (mmol/l)[20] and RPE were measured. Exercise-onset 20- and 60-second changes in VE, RR, VO_2 and Vt were calculated. These changes reflect the speed of accommodation of the respiratory system to initiation of exercise. In part 2, ventilatory function during exercise was re-evaluated after a 6-month follow-up. The same absolute workload was applied during this second exercise test.

Statistical analysis

All calculations were performed using SPSS® v. 22.0 (IBM Corporation, USA). Data were expressed as means±SD. Shapiro-Wilk tests confirmed normal distribution of data ($p>0.05$). For non-time-dependent variable comparisons between groups one-way ANOVA or Chi-Square analysis was

applied. To assess differences between control group vs. exercise intervention group during follow-up, two-way ANOVA repeated measures, with treatment and time as the two factors, was applied. Within these analyses corrections for multiple comparisons were made (Bonferroni). The observed statistical power (α) was calculated for each comparison. Univariate relationships between parameters were examined by Pearson correlations. Statistical significance was set at $p<0.05$ (2-tailed), and observed statistical power was calculated for each comparison.

Results

PART 1

Subject characteristics

Thirty-seven pwMS (n=10 with SPMS, n=20 with RRMS, n=3 with PPMS, n=1 with PRMS, MS type was not determined in three pwMS) and 15 healthy participants were included in part 1 (Table 1). Between groups subject characteristics were comparable ($p>0.05$), except for medication intake.

Ventilatory response to exercise

As expected, cycling power output during exercise testing was significantly higher in healthy participants vs. pwMS ($p<0.001$, Table 2). Steady-state exercise HR ($p=0.58$), %predicted maximal HR ($p=0.70$) and blood lactate content ($p=0.97$) was similar between groups indicating equal relative exercise intensities between groups.

At rest, a significantly different Vd/Vt ratio was observed between groups ($p=0.04$), while trends for differences between groups were found for VE/VCO_2 ($p=0.05$) and RR ($p=0.06$) (Table 2).

During steady-state exercise, significant differences between groups were found for VO_2, Vd/Vt ratio, VE/VO_2, VE/VCO_2, $PETO_2$, $PETCO_2$, VO_2/HR, RPE, exercise-onset VO_2 change ($p<0.05$), and a trend for a difference in VCO_2 ($p=0.06$) (Table 2). Exercise-onset 20- and 60-second changes in VE, RR, and Vt were comparable between groups ($p>0.05$).

Correlations

Correlations (Figure 2) between exercise intensity (steady-state exercise blood lactate content) or exercise RPE, and ventilatory parameters during exercise which significantly deviated in pwMS, were examined. Significant correlations were found between exercise blood lactate content and VE/VO_2 ($r=0.42$), $PETO_2$ ($r=0.37$) ($p<0.05$). Exercise blood lactate content did not correlate with subject characteristics (age, gender, BMI, EDSS, physical activity level) ($p>0.10$). Significant correlations were found between exercise RPE and VE/VO_2 ($r=0.32$), VE/VCO_2 ($r=0.35$), $PETCO_2$ ($r=-0.28$) ($p<0.05$).

Exercise RPE did not correlate with subject characteristics (age, gender, BMI, $p>0.10$), except physical activity level ($r=-0.29$) and EDSS ($r=0.50$) ($p<0.05$).

PART 2

Subject characteristics

Sixteen pwMS (n=2 with SPMS, n=12 with RRMS, n=1 with PPMS, MS type was not determined in two pwMS) followed a 6-month training intervention and 11 pwMS (n=1 with SPMS, n=6 with RRMS, n=2 with PPMS, n=1 with PRMS, MS type was not determined in one pwMS) received usual care (Table 3). Between groups subject characteristics were comparable ($p>0.05$). No adverse events related to exercise training occurred during the 6-month follow-up.

Ventilatory response to exercise

Baseline exercise responses were comparable between groups ($p>0.05$) (Table 4). In total group, steady-state exercise RPE decreased significantly ($p<0.05$), but with significant greater magnitude in intervention vs. control participants ($p<0.05$). Group*time interaction effects were found for steady-state exercise HR and blood lactate content, in favour of the intervention group ($p<0.05$). In total group steady-state exercise Vd/Vt ratio decreased significantly ($p<0.05$) without significant group*time interaction effect ($p=0.07$). In total group steady-state exercise RR did not change significantly ($p>0.05$), while a significant group*time interaction effect was found ($p=0.04$). No other changes were observed.

Discussion

In this study, a disturbed ventilatory function during endurance exercise was observed in patients with multiple sclerosis (pwMS). More specifically, elevated dead space/tidal volume (Vd/Vt) ratios, equivalents for oxygen uptake (VE/VO_2) and carbon dioxide (VE/VCO_2) and end-tidal oxygen pressures ($PETO_2$), and lowered end-tidal pressures for carbon dioxide ($PETCO_2$) were found in MS, collectively indicating a ventilation-perfusion mismatch during exercise. This ventilation-perfusion mismatch persisted following a 6-month training intervention.

Elevated VE/VO_2 and VE/VCO_2 ratios during exercise in pwMS suggest a reduced gas exchange efficiency for O_2 and CO_2. Even at rest a slight anomaly was found for VE/VCO_2 in pwMS. In extent, exercise $PETO_2$ and $PETCO_2$ were significantly elevated and lowered, respectively, in pwMS. These data are in line with those from previous studies,[11-13] but with proper matching of exercise intensities and subject characteristics between groups. It could be hypothesized that an abnormal diffusion capacity, arterial pulmonary hypertension, diaphragmatic dysfunction or disturbed respiratory coordination could lead to such ventilatory dysfunction during exercise in MS.

To explain a reduced ventilatory gas exchange efficiency, likely caused by ventilation-perfusion mismatching, an abnormal diffusion capacity could be proposed (for an overview of the following hypotheses to explain a ventilation-perfusion mismatch in MS: see Figure 3). A significantly lower diffusion capacity has been observed in pwMS.[2,3] A compromised gas exchange leads to elevations in VE/VCO_2 and VE/VO_2, and altered $PETO_2$ and $PETCO_2$. However, cardiovascular dysfunction might also lead to ventilation-perfusion inequalities in pwMS. Significant left ventricular dysfunction is present at rest in pwMS.[21] Moreover, we recently observed an abnormal cardiac autonomic control during exercise in pwMS: such disturbed cardiac autonomic control could lead to a lowered stroke volume during exercise.[22] In the present study and in previous observations,[11] a significant lower oxygen pulse during exercise was observed in pwMS vs. healthy participants, indicating a lowered stroke volume and/or peripheral oxygen extraction capacity in pwMS. Such impaired left ventricular function during exercise could lead to arterial pulmonary hypertension. This would further elevate

VE/VCO_2 and alter $PETCO_2$ during exercise.[23] However, primary pulmonary arterial hypertension could be present in pwMS, especially when receiving interferon therapy, without evidence for left ventricular dysfunction.[24] Whether diaphragmatic dysfunction or disturbed respiratory coordination would contribute to ventilation-perfusion mismatch during exercise in pwMS remains difficult to determine.[25,26] In the present study, (changes in) tidal volumes were preserved in pwMS during exercise. It might thus be speculated that diaphragmatic contractility/function or respiratory coordination is normal in pwMS, although no inspiratory muscle strength, diaphragmatic muscle function, or respiratory coordination tests were executed. In case of severe ventilation-perfusion mismatch hypoxemia could develop which further leads to an increased ventilatory drive. (Exercise-onset changes in) Tidal volume and respiratory rate were similar between pwMS and healthy participants during exercise, while (exercise-onset change in) VO_2 was greater in healthy participants. This indicates that pwMS experience relative hyperventilation during (initiation of) exercise. According to previous observations pwMS could eventually experience desaturation during exercise.[12] Determining the aetiology of a ventilation-perfusion mismatch in pwMS remains however speculative in the present study due to absence of echocardiographic analyses, measurement of oxygen saturation, arterial partial O_2 and CO_2 and pulmonary blood pressures.

Correlations between elicited exercise intensity (exercise blood lactate content) and VE/VO_2 ($r=0.42$), $PETO_2$ ($r=0.37$) ($p<0.05$) were found in part 1. Exercise blood lactate content did not correlate with subject characteristics ($p>0.10$). It thus seems that an impaired O_2 uptake efficiency, which is specifically present in MS, is related to anaerobic metabolism during exercise. These data are in line with previous observations of relations between exercise tolerance and pulmonary function (although at rest) in pwMS.[10] In the present study significant correlations were observed between ratings of perceived exertion (RPE) during exercise and several ventilatory parameters that significantly deviated in MS during exercise (VE/VO_2, VE/VCO_2, $PETCO_2$). In addition to disability level (based on EDSS), ventilatory dysfunction during exercise could thus significantly elevate exercise RPE in pwMS. A ventilation-perfusion mismatch during exercise in pwMS could thus lower exercise

tolerance and/or elevate exercise RPE. However, univariate correlations do not necessarily indicate causal relationships between parameters.

A ventilation-perfusion mismatch during endurance exercise in pwMS was not remediated by a 6-month training intervention. Despite significant improvements in exercise tolerance (decreases in exercise blood lactate level and heart rate at similar workload) and lower exercise RPE, ventilatory anomalies remained present. Changes in training modalities or addition of other medical interventions could be mandatory to effectively improve/restore ventilatory function during exercise in pwMS. For example, inspiratory and expiratory muscle training significantly improves pulmonary function at rest[27,28] and application of breathing-enhanced upper extremity exercises improves resting pulmonary function in pwMS.[29] In these studies, the effect of inspiratory muscle training against low-to-moderate inspiratory resistance as an addition to endurance exercise training (for 10 weeks) was explored,[27] the effect of expiratory muscle training against low-to-high expiratory resistance (for eight weeks) was studied,[28] or the impact of breathing exercises combined with certain upper body movements (for six weeks)[29] was examined. However, data on ventilatory function during exercise were not collected in these studies. It thus remains uncertain whether such interventions could lead to improvements in ventilation-perfusion match during exercise in MS. In addition, maybe greater exercise training intensities should have been applied to increase the likelihood for improvements in ventilatory function in pwMS. However, as long as the aetiology of a ventilation-perfusion mismatch during exercise in MS remains elusive, it is difficult to propose effective treatments. It thus follows that the aetiology for ventilation-perfusion mismatch during exercise in pwMS should be examined in greater detail.

From this study, certain clinical implications emerged. Given the presence of ventilation-perfusion mismatch during exercise, which is significantly related to exercise tolerance and RPE, the systematic examination of the pulmonary/cardiovascular system at rest and during exercise is recommended in pwMS. In extent, interventions to improve gas exchange efficiency during exercise in MS should be developed/examined.

This study was limited by a lack of resting spirometry and respiratory muscle strength assessment. Moreover, for certain parameter comparisons between groups a low statistical power was observed.

Conclusions

During endurance exercise a ventilation-perfusion mismatch is present in patients with MS. This ventilatory anomaly is related to exercise intolerance and worse exercise sensations. A long-term endurance-resistance training intervention is ineffective to remediate this ventilatory anomaly in patients with MS.

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Tables and Figures

Table 1 Subject characteristics in part 1.

	MS patients	healthy subjects	p-value
general characteristics			
n	37	15	
age (y)	48 ± 10	50 ± 10	0.50
males (n of total group)	15	7	0.76
body height (cm)	170 ± 8	175 ± 9	0.09
body weight (kg)	73 ± 14	75 ± 13	0.66
body mass index (kg/m²)	25.3 ± 4.7	24.5 ± 2.6	0.56
disease characteristics			
EDSS	3.1 ± 1.3	-	
type of MS (n)*			
SPMS	10	-	
RRMS	20	-	
PPMS	3	-	
PRMS	1	-	
physical activity score (MET/h/week)	18.7 ± 15.9	14.7 ± 10.6	0.38
medication			
Beta-blocker (n)	1	1	
Glatiramer acetate (n)	4	0	
Natiluzimab (n)	5	0	
Interferon (n)	16	0	
Muscle relaxing drug (n)	2	0	
Analgesic (n)	6	0	
ACE-inhibitor (n)	0	1	
Statin (n)	2	3	
Antiplatelet (n)	3	0	
Non-steroid anti-inflammatory drug (n)	2	0	
Proton pump inhibitor (n)	4	0	
Thyroid hormone replacement drug (n)	1	0	
Anti-depressant drug (n)	5	0	
Benzodiazepine (n)	5	0	

Data are expressed as means±SD. Abbreviations: EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; MET, metabolic equivalent.
*Type of MS was not established in three patients.

Table 2 Ventilatory function during exercise in patients with MS vs. healthy subjects (part 1).

	MS patients	healthy subjects	p-value	observed power (α)
Cycling power output (W)	41 ± 14	62 ± 21	<0.001	0.97
Resting VCO_2 (ml/min)	240 ± 84	275 ± 75	0.16	0.25
Resting VO_2 (ml/min)	287 ± 98	317 ± 77	0.28	0.16
Resting VE (l/min)	9.1 ± 2.9	10.1 ± 2.7	0.23	0.23
Resting Vt (l/min)	0.65 ± 0.25	0.64 ± 0.16	0.91	0.06
Resting RR (breaths/min)	15 ± 3	17 ± 3	0.06	0.65
Resting Vd/Vt ratio (%)	17.0 ± 5.0	13.9 ± 4.4	0.04	0.35
Resting VE/VO_2	27.2 ± 3.6	26.2 ± 3.7	0.34	0.08
Resting VE/VCO_2	32.5 ± 3.6	30.3 ± 3.2	0.05	0.32
Resting $PETO_2$ (KPa)	14.8 ± 0.6	14.9 ± 0.6	0.68	0.08
Resting $PETCO_2$ (KPa)	4.4 ± 0.5	4.6 ± 0.4	0.23	0.20
Resting HR (bts/min)*	78 ± 12	79 ± 12	0.90	0.08
Resting VO_2/HR (ml/beat)*	3.7 ± 1.2	4.0 ± 1.1	0.43	0.27
Exercise VCO_2 (ml/min)	920 ± 265	1085 ± 325	0.06	0.48
Exercise VO_2 (ml/min)	998 ± 280	1168 ± 261	0.04	0.44
Exercise VE (l/min)	27.4 ± 7.7	29.0 ± 10.0	0.55	0.12
Exercise Vt (l/min)	1.38 ± 0.38	1.52 ± 0.47	0.28	0.27
Exercise RR (breaths/min)	20 ± 4	19 ± 3	0.35	0.20
Exercise Vd/Vt ratio (%)	17.6 ± 3.5	13.3 ± 1.9	<0.001	0.97
Exercise VE/VO_2	25.9 ± 3.3	22.7 ± 3.8	0.005	0.61
Exercise VE/VCO_2	28.0 ± 2.6	24.6 ± 2.6	<0.001	0.95
Exercise $PETO_2$ (KPa)	14.3 ± 0.7	13.8 ± 0.7	0.04	0.39
Exercise $PETCO_2$ (KPa)	5.2 ± 0.5	5.8 ± 0.5	0.001	0.90
Exercise HR (bts/min)*	108 ± 17	105 ± 13	0.58	0.18
Exercise %predicted maximal HR*	63 ± 8	62 ± 6	0.70	0.09
Exercise blood lactate (mmol/l)	3.1 ± 0.8	3.1 ± 1.1	0.97	0.08
Exercise VO_2/HR (ml/beat)	9.3 ± 2.6	11.2 ± 2.6	0.03	0.67
Ratings of perceived exertion	11.4 ± 1.8	9.7 ± 1.4	0.002	0.77
20-second change in VE (l/min)	5.2 ± 4.3	6.2 ± 3.4	0.42	0.10
20-second change in Vt (l/min)	0.20 ± 0.29	0.27 ± 0.32	0.45	0.14
20-second change in RR (breaths/min)	3.1 ± 3.9	2.1 ± 4.0	0.40	0.15
20-second change in VO_2 (ml/min)	251 ± 153	319 ± 125	0.13	0.19
60-second change in VE (l/min)	9.5 ± 5.2	11.3 ± 3.7	0.23	0.07
60-second change in Vt (l/min)	0.42 ± 0.38	0.61 ± 0.42	0.12	0.10
60-second change in RR (breaths/min)	3.7 ± 4.4	1.5 ± 4.5	0.11	0.25
60-second change in VO_2 (ml/min)	495 ± 225	723 ± 213	0.002	0.77

Data are expressed as means±SD. Abbreviations: VO_2, oxygen uptake; HR, heart rate; bts, beats; VE, expiratory volume; VCO_2, carbon dioxide output, Vd, dead space volume; Vt, tidal volume; PET, end-tidal pressure; RR, respiratory rate.

*Data from subjects taking beta blockers were removed (n=2).

Table 3 Subject characteristics in part 2.

	intervention	control	p-value
general characteristics			
n	16	11	
age (years)	46 ± 11	48 ± 10	0.76
males (n in total group)	6	5	0.71
body height (cm)	170 ± 8	172 ± 7	0.49
body weight (kg)	76 ± 17	69 ± 11	0.26
body mass index (kg/m²)	26.1 ± 5.2	23.4 ± 4.0	0.15
disease characteristics			
EDSS	3.0 ± 1.5	3.0 ± 1.3	0.95
type of MS (n)*			0.43
SPMS	2	1	
RRMS	12	6	
PPMS	1	2	
PRMS	0	1	
medication			
Beta-blocker (n)	0	1	
Glatiramer acetate (n)	3	1	
Natiluzimab (n)	4	1	
Interferon (n)	6	5	
Muscle relaxing drug (n)	1	1	
Analgesic (n)	4	0	
Statin (n)	2	0	
Antiplatelet (n)	2	0	
Non-steroid anti-inflammatory drug (n)	1	0	
Proton pump inhibitor (n)	1	1	
Thyroid hormone replacement drug (n)	1	0	
Anti-depressant drug (n)	4	0	
Benzodiazepine (n)	2	2	

Data are expressed as means±SD. Abbreviations: EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; MET, metabolic equivalent.
*Type of MS was not established in three patients.

Table 4 Impact of long-term exercise intervention on ventilatory function during exercise (part 2).

	Initial test		Six months of follow-up		time*group interaction	observed power (α)
	control subjects (n=11)	intervention subjects (n=16)	control subjects (n=11)	intervention subjects (n=16)	p-value	
Cycling power output (W)	42 ± 12	43 ± 17	42 ± 12	43 ± 17	-	
Exercise VCO_2 (ml/min)	922 ± 281	957 ± 250	912 ± 201	881 ± 255	0.36	0.15
Exercise VO_2 (ml/min)	968 ± 260	1027 ± 300	958 ± 231	955 ± 260	0.40	0.13
Exercise VE (l/min)	27.2 ± 2.0	29.2 ± 7.9	26.7 ± 5.4	26.9 ± 7.9	0.37	0.14
Exercise Vt (l/min)	1.3 ± 0.4	1.5 ± 0.4	1.4 ± 0.6	1.4 ± 0.4	0.18	0.27
Exercise RR (breaths/min)	21 ± 3	20 ± 3	20 ± 4	20 ± 4	0.76	0.06
Exercise Vd/Vt ratio (%)	19.0 ± 2.6	17.0 ± 4.1	15.1 ± 2.7	14.8 ± 3.2	0.07	0.44
Exercise VE/VO_2	26.6 ± 2.2	26.9 ± 3.1	25.9 ± 2.6	25.9 ± 3.1	0.79	0.06
Exercise VE/VCO_2	28.0 ± 2.5	28.6 ± 2.4	26.9 ± 2.6	28.1 ± 3.3	0.51	0.10
Exercise $PETO_2$ (KPa)	14.3 ± 0.5	14.6 ± 0.6	14.2 0.6	14.3 ± 0.6	0.59	0.08
Exercise $PETCO_2$ (KPa)	5.4 ± 0.5	5.0 ± 0.4	5.5 ± 0.5	5.2 ± 0.6	0.80	0.06
Exercise HR (bts/min)*	106 ± 21	113 ± 18	111 ± 18	107 ± 12	0.03	0.58
Exercise %predicted maximal HR*	61 ± 11	65 ± 7	64 ± 9	62 ± 5	0.03	0.59
Exercise VO_2/HR (ml/beat)*	8.9 ± 2.8	9.2 ± 2.6	8.5 ± 1.8	9.0 ± 2.7	0.65	0.07
Exercise lactate (mmol/l)	3.4 ± 0.6	3.2 ± 0.8	3.6 ± 1.0	2.5 ± 0.7	0.01	0.72
Ratings of perceived exertion	10.7 ± 2.4	11.7 ± 1.6	10.7 ± 2.2	9.8 ± 1.7	0.02	0.69
20-second change in VE (l/min)	5.1 ± 3.4	6.2 ± 5.2	5.0 ± 4.5	7.2 ± 4.0	0.50	0.21
20-second change in Vt (l/min)	0.1 ± 0.2	0.2 ± 0.4	0.2 ± 0.3	0.2 ± 0.2	0.50	0.10
20-second change in RR (breaths/min)	4.2 ± 3.4	2.9 ± 2.9	1.4 ± 3.9	3.6 ± 2.9	0.04	0.54
60-second change in VE (l/min)	9.8 ± 5.9	9.1 ± 4.4	10.1 ± 4.4	11.0 ± 4.9	0.46	0.11
60-second change in Vt (l/min)	0.5 ± 0.6	0.4 ± 0.2	0.5 ± 0.2	0.4 ± 0.3	0.97	0.05

Data are expressed as means±SD and represent ventilatory parameters before and after six months of exercise intervention (see Methods).

Abbreviations: VO_2, oxygen uptake; HR, heart rate; bts, beats; VE, expiratory volume; VCO_2, carbon dioxide output, Vd, dead space volume; Vt, tidal volume; PET, end-tidal pressure; RR, respiratory rate.

*Data from patients taking beta blockers were removed (n=1).

Figure 1 Flowchart of part 2.

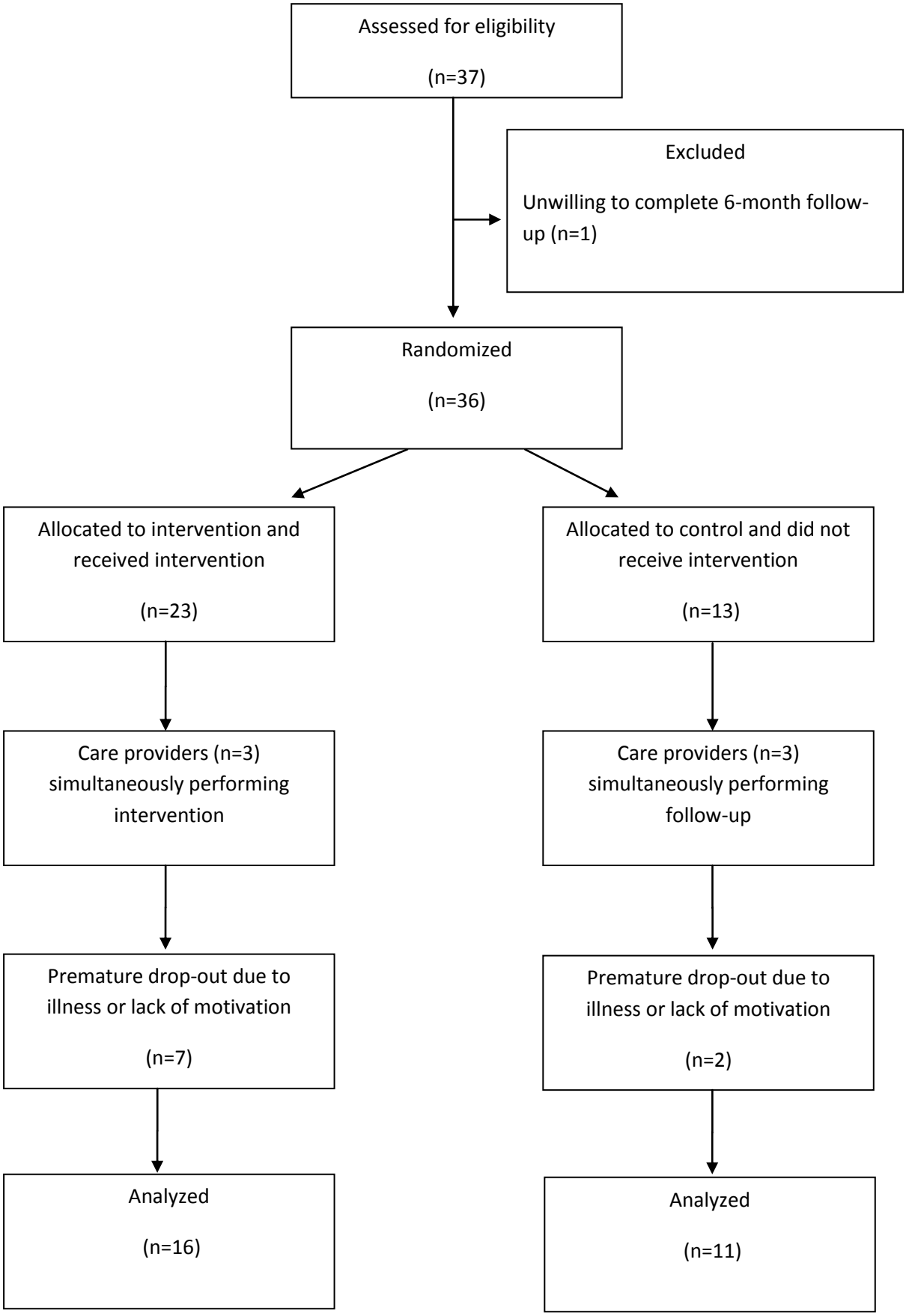
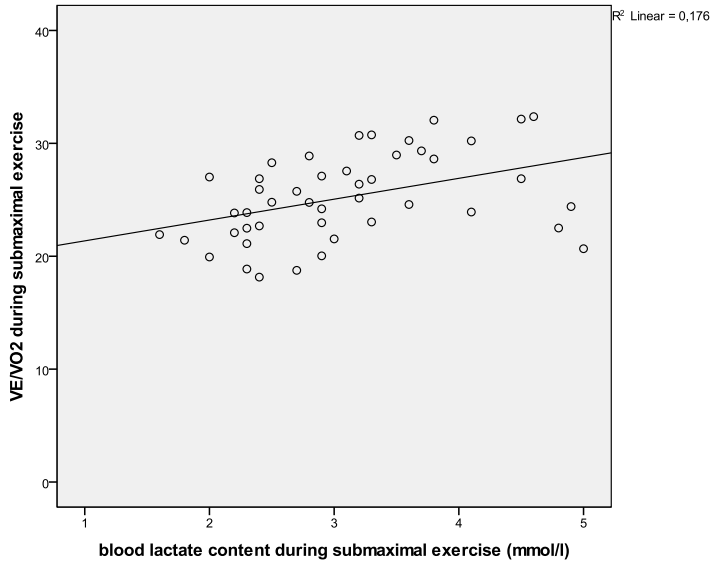
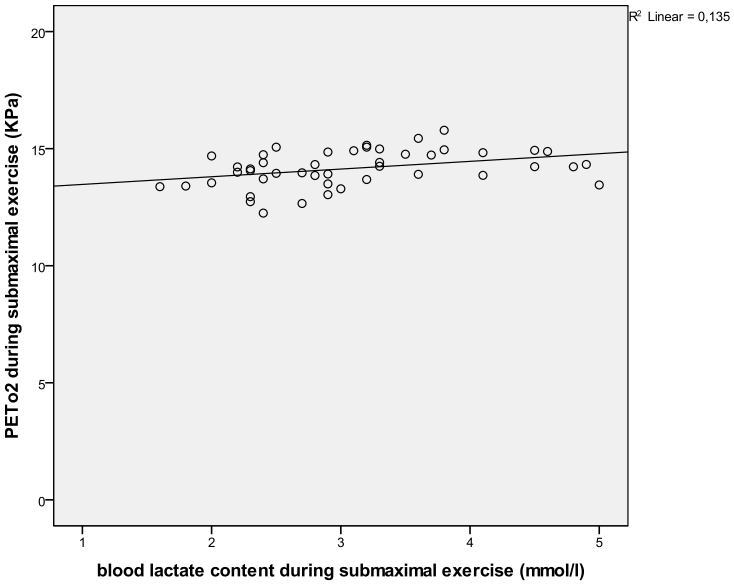
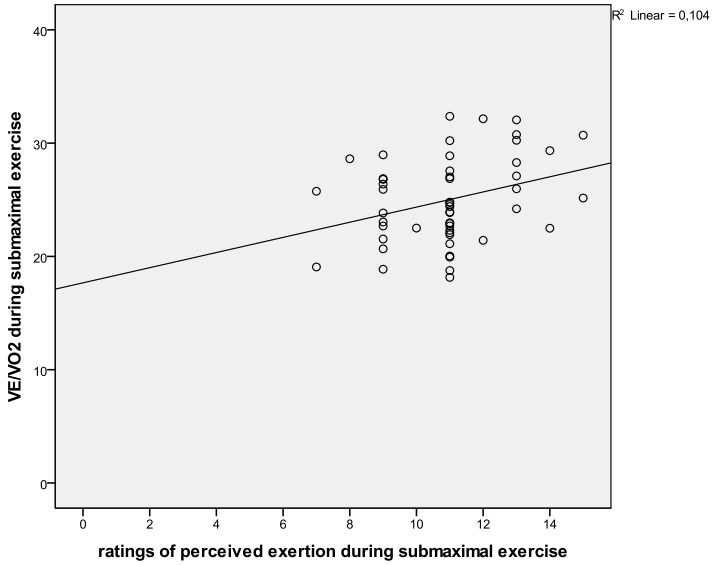
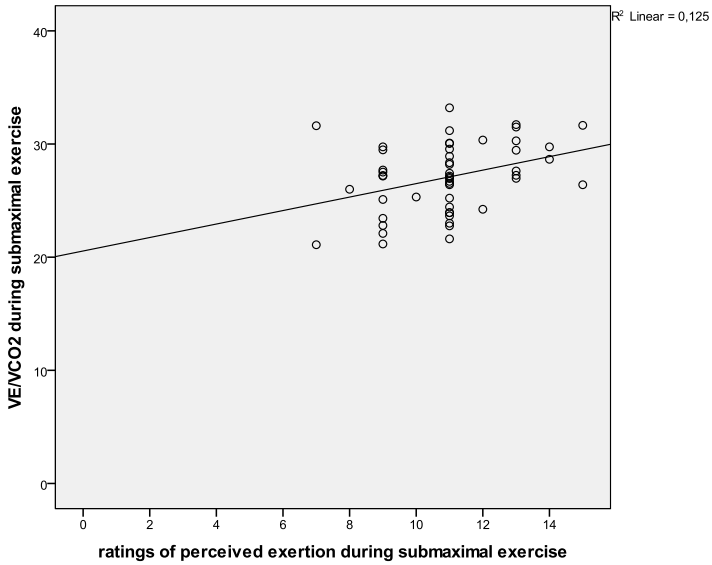


Figure 2 Relations between anomalous ventilatory responses during submaximal exercise in patients with MS and markers of exercise tolerance or ratings of perceived exertion.









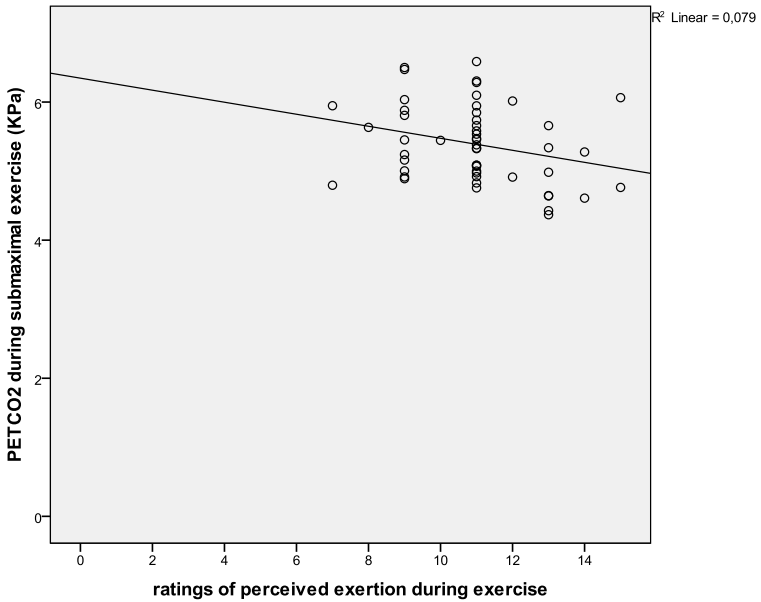


Figure 3 Hypothesized mechanisms for ventilation-perfusion mismatch and its consequences during exercise in patients with MS