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Is long-term exercise intervention effective to improve cardiac autonomic control during exercise in subjects with multiple sclerosis? A randomized controlled trial.

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**Abstract***Background*

Patients with multiple sclerosis (MS) suffer from a disturbed cardiac autonomic control during exercise (based on heart rate (HR) changes during exercise), which affects exercise tolerance. Whether long-term exercise intervention improves HR changes during exercise in patients with MS remains unknown.

*Aim*

To examine whether long-term exercise intervention improves HR changes during exercise, and correlates with improvements in exercise tolerance, in patients with MS.

*Design*

Randomized controlled trial.

*Setting*

University rehabilitation facility.

*Population*

Twenty-three patients with MS were randomly assigned to six months of follow-up (n=9) or six months of exercise training (n=14, 54-60 training sessions).

*Methods*

At baseline and after three and six months of follow-up, exercise-onset (first 20 and 60 seconds) and –offset (1-minute recovery) heart rate (HR) change was determined during a constant-load exercise test: these data reflect the (re)activation of the (para)sympathetic nervous system at initiation and/or

cessation of exercise. Blood lactate, HR, oxygen uptake, expiratory volume and ratings of perceived exertion (RPE) were assessed during exercise as indicators for exercise tolerance.

### *Results*

Exercise-onset and -offset HR and exercise tolerance did not change during follow-up in the control group ( $p>0.05$ ). In the exercise intervention group, blood lactate content and RPE during exercise decreased significantly (group\*time interaction effect  $p<0.05$ ), but exercise-onset and -offset HR did not change ( $p>0.05$ ). No correlations were found between changes in exercise tolerance and changes in exercise-onset and -offset HR ( $p>0.05$ ).

### *Conclusion*

In patients with MS, long-term exercise intervention does not improve HR changes during exercise, despite improvements in exercise tolerance, indicating that cardiac autonomic control during exercise is not easily improved by exercise intervention in patients with MS.

### *Clinical rehabilitation impact*

This study indicates that patients with MS suffer from a disturbed cardiac autonomic control during exercise, based on heart rate changes, which is not easily remediated by exercise intervention. Because a disturbed cardiac autonomic control is related to exercise intolerance in MS, it should further be explored how to remediate this anomaly through exercise intervention or other approaches.

Keywords: multiple sclerosis, exercise intervention, heart rate, autonomic control

## Introduction

A disturbed autonomic control is often present in patients with multiple sclerosis (MS),<sup>1-4</sup> which is manifested by inappropriate sweating and gastrointestinal and cardiovascular dysfunction. It is speculated that demyelinating plaques damage the vasomotor centres in the brainstem and/or interfere with autonomous nervous system descending fibers in the spinal cord.<sup>1-4</sup>

A disturbed cardiac autonomic control can be observed during constant-workload exercise testing by evaluating changes in heart rate (HR).<sup>5</sup> More specifically, the HR increase during the first 20 seconds of exercise is smaller in subjects with MS vs. healthy controls, indicating that the withdrawal of the tonic vagal activity after initiation of exercise is impaired in MS patients.<sup>6</sup> Moreover, a smaller HR increase during the first 20 seconds of exercise correlates with a reduction in walking capacity ( $r=0.64$ ,  $p<0.01$ ) in subjects with MS.<sup>5</sup> A disturbed cardiac autonomic control thus might be one of the reasons for an impaired exercise tolerance in MS patients,<sup>5</sup> which already was shown in cardiovascular disease patients.<sup>7</sup>

Long-term exercise intervention improves cardiac autonomic control at rest and during exercise, at least in animal studies and healthy subjects, which is characterized by the development of a pre-dominance of the parasympathetic component over the sympathetic component, leading to a lowered resting HR and exercise HR at the same absolute workload, and faster HR recovery after exercise.<sup>8-10</sup>

In patients with MS however, it remains unclear whether exercise intervention is effective to improve cardiac autonomic control during exercise. A recent study examined for the first time the impact of a 12-week exercise intervention on exercise-onset HR change in patients with MS, although HR

measurements were made during training sessions (which might lack proper standardization), HR was assessed every two minutes (not early enough to detect detailed differences), and HR recovery after exercise was not assessed.<sup>11</sup> Moreover, relations between changes in cardiac autonomic control during exercise and changes in exercise tolerance were not explored.<sup>11</sup>

Because patients with MS are often included in rehabilitation programs to improve exercise tolerance, it is relevant to evaluate the impact of such intervention on cardiac autonomic control during exercise. Such study further explores the etiology of exercise intolerance in patients with MS, and the impact of exercise intervention on these etiological factors.

In this study, it is examined whether a long-term exercise intervention affects cardiac autonomic control during exercise in patients with MS. We hypothesized that improvements in cardiac autonomic control result from long-term exercise training in subjects with MS, and that such enhancements correlate with improvements in exercise tolerance.

## **Materials and methods**

### *Subjects*

Twenty-three subjects with multiple sclerosis (MS) completed this study. Originally, 39 subjects were included in this study (n=15 in control group, n=24 in intervention group), but 16 subjects were lost during follow-up (see Figure 1). An a-priori study sample size calculation was not executed, but according to previous studies such sample (n=23) is sufficient to detect statistically significant and clinically relevant changes in cardiac autonomic control.<sup>8,11</sup> Subjects had been diagnosed for at least 12 months (mean disease duration of 10.1±7.2 years, range 2-23 years) and were sedentary (<2 hours of sports activities or exercise training per week). None of the subjects took heart rate (HR) altering medication. Subjects were informed about the nature and risks of the experimental procedures before their written informed consent was obtained. This study was approved by the medical ethical committee of Hasselt University.

### *Study design*

This was a prospective randomized controlled trial. Results were revealed to the subjects after completion of the study. Following Expanded Disability Status Scale (EDSS) determination<sup>12</sup> and medication intake screening by a neurologist, subjects were randomly assigned to a 6-month control follow-up or a 6-month exercise intervention by sealed envelope in a 1:2 (usual care : exercise intervention) ratio. Considering the smaller total sample size in this study, this was done to increase the likelihood for finding significant changes in exercise-onset and -offset HR changes within the intervention group. Patients could not be blinded to treatment allocation, but assessors were.

### *Outcome measures*

Primary outcome measures in this study were resting HR, 20-second and 60-second exercise-onset HR, and HR recovery. Secondary outcome measures were exercise blood lactate content, ratings of perceived exertion, oxygen uptake and expiratory volume.

### *Exercise test*

Subjects performed a cardiopulmonary exercise test on a electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany). Subjects were advised not to perform any exercise two days before or at the day of testing, and only eat a light meal at least two hours prior to testing. At the 6-month follow-up evaluation at least 48 hours of recovery from the final training session was provided to the subjects. The baseline and follow-up exercise test was executed at exactly the same time of day.

Pulmonary gas exchange was continuously measured breath-by-breath with a mass spectrometer and volume turbine system (Jaeger Oxycon, Erich Jaeger GmbH, Germany). During the exercise test, oxygen uptake ( $\text{VO}_2$ , ml/min) and expiratory volume (VE, l/min) was assessed breath-by-breath, after



which these data were averaged every 10 seconds. Heart rate (HR) was continuously monitored by 12-lead ECG device.

At the end of the exercise bout, capillary blood samples were obtained from the fingertip to analyze blood lactate concentrations (mmol/l), using a portable lactate analyzer (Accutrend Plus®, Roche Diagnostics Limited, Sussex, UK).<sup>13</sup> At the end of the 6-min exercise bout ratings of perceived exertion (RPE) was scored by the subject on a 6-20 Borg scale.

Subjects were seated on bike for three minutes to obtain resting data. Next, subjects were instructed to cycle at a rate of 70 rpm, against a resistance corresponding to 25% of predicted cycling power output ( $W_{max}$ ) for six minutes.<sup>14</sup> This workload was selected because exercise intensities were then elicited that could be tolerated in patients with MS and a steady-state exercise HR was achieved.<sup>14</sup> After six minutes of cycling subjects remained seated on bike for an additional six minutes. Predicted  $W_{max}$  was based on gender, age, body weight and height.<sup>15</sup> The selected workload (W) remained the same during the 6-month follow-up exercise test.

#### *Exercise-onset and -offset HR change*

Resting HR was calculated as the averaged HR during the final minute of rest before exercise. Exercise HR was defined as the averaged HR between 5<sup>th</sup> and 6<sup>th</sup> minutes of cycling. In all subjects, a steady-state HR was achieved within 4-5 minutes of exercise. To determine the exercise-onset HR change, we calculated the difference between resting HR (averaged HR during final minute of rest before exercise) and HR measured at exactly 20 seconds of exercise. It is agreed that the first 20 seconds of exercise is characterized by predominantly vagal tone withdrawal.<sup>16</sup> We then calculated the difference between resting HR (averaged HR during final minute of rest before exercise) and HR measured at exactly 60 seconds of exercise. At this timeframe activation of sympathetic nervous system is expected.<sup>16</sup> To determine the exercise-offset HR change, we calculated the difference between end-exercise HR (averaged HR between 5<sup>th</sup> and 6<sup>th</sup> minute of exercise), and HR measured at exactly one minute after exercise.<sup>17</sup> This timeframe represents the re-activation of the parasympathetic nervous system.

### *Exercise intervention*

Participants from the intervention group followed a supervised 6-month combined endurance-resistance training program at a rate of five sessions per two weeks, on top of their current home-based physical activities. Endurance exercises (on bike and treadmill) were always executed first, followed by resistance exercises (three upper body and three lower body exercises). Each session started with endurance exercise training, consisting of cycling and treadmill walking or running (on Technogym® deviced). Session duration and exercise intensity increased as the intervention progressed, starting from 1x6 min/session to 3x10 min/session, at a mild-to-moderate workload corresponding to 12-14 ratings of perceived exertion on 20-point Borg scale and according to individual capabilities, depending on heart rate and disability level. The second part consisted of resistance training (leg press, leg curl, leg extension, vertical traction, arm curl, chest press, on Technogym® devices). Resistance training of the lower limbs was performed unilaterally, due to bilateral strength differences between the legs of patients with MS. To improve maximal power as well as to reduce muscle work fatigue, exercise workload and sets of repetitions gradually increased during intervention, from 1x10 repetitions to 4x15 repetitions, at a mild-to-moderate workload corresponding to 12-14 ratings of perceived exertion on 20-point Borg scale and according to individual capabilities. During the entire training period, subjects were strongly encouraged and supervised by the instructors to increase the training load in the following session if they felt competent of performing more than the prescribed load. These incentives led to a systematic increase of the training load 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. The sessions were finished by stretching, and level of perceived exertion (20-point Borg scale) was recorded. All subjects completed >54 out of 60 training sessions.

### *Statistical analysis*

All calculations were performed using the Statistical Package for the Social Sciences version 18.0 (SPSS®). Data are expressed as means±SD. According to Shapiro-Wilk tests data were normally distributed. For non-time-dependent variable comparisons one-way ANOVA or Chi-Square analysis was applied. Within-group changes of parameters were examined by paired-sample T-tests. Group\*time interaction effects were evaluated by one-way ANOVA repeated measures. Univariate relationships between parameters were examined by Pearson correlations. General linear models were created to examine relations between changes in exercise-onset 20-second and 60-second HR, and HR recovery after exercise, during follow-up (independent variables), and treatment allocation (control vs. intervention: dependent variable), but with correction for changes in exercise blood lactate content during follow-up (covariate) (to correct for changes in relative exercise intensities). Statistical significance was set at  $p < 0.05$  (2-tailed).

## Results

### *Subject characteristics*

In Tables 1 and 2, subjects characteristics are displayed. Between groups no significant baseline differences were found ( $p > 0.05$ ). The following neurologic medications were prescribed to the subjects: natalizumab (intervention  $n=5$ , control  $n=3$ ), anti-epileptic (intervention  $n=3$ , control  $n=1$ ), interferon (intervention  $n=6$ , control  $n=6$ ), benzodiazepine (intervention  $n=2$ , control  $n=3$ ), selective serotonin reuptake inhibitor (intervention  $n=4$ , control  $n=1$ ), glatiramer acetate (intervention  $n=3$ , control  $n=1$ ), tricyclic antidepressant (intervention  $n=2$ , control  $n=1$ ), muscle relaxing drug (intervention  $n=3$ ,

control n=1). Medication intake was not different between groups ( $p>0.05$ ). No significant impact of pharmacotherapy was found on baseline resting HR and HR responses to exercise ( $p>0.05$ ).

#### *Heart rate responses to exercise and exercise tolerance*

No significant changes in HR responses to exercise were found in the control (change in 20 –and 60-second exercise-onset HR, and HR recovery;  $-0.4\pm 8.0$  bts/min,  $0.7\pm 6.9$  bts/min,  $1.4\pm 7.9$  bts/min, respectively) and intervention (change in 20 –and 60-second exercise-onset HR, and HR recovery;  $-2.3\pm 6.7$  bts/min,  $0.3\pm 6.3$  bts/min,  $0.3\pm 7.6$  bts/min, respectively) patients during follow-up, nor were group\*time interaction effects present ( $p>0.05$ , see Table 2). In the intervention group, resting and exercise blood lactate content, and exercise RPE decreased significantly during follow-up (by  $-0.6\pm 0.7$  mmol/l,  $-0.7\pm 0.9$  mmol/l, and  $-1.9\pm 1.8$ , respectively,  $p<0.05$ ), but not in the control group (by  $-0.2\pm 0.8$  mmol/l,  $0.2\pm 0.6$  mmol/l, and  $0.1\pm 1.9$ , respectively,  $p<0.05$ ). Group\*time interaction effects were found for changes in exercise blood lactate content and exercise RPE ( $p<0.05$ , see Table 2). Interferon therapy affected the change in HR response within the first 60 seconds (change of  $3.4\pm 7.0$  bts/min in interferon users vs. change of  $-2.8\pm 3.6$  bts/min in non-users,  $p=0.01$ ) during follow-up, as well as change in exercise blood lactate content (change of  $0.0\pm 0.6$  mmol/l in interferon users vs. change of  $-0.8\pm 1.0$  mmol/l in non-users,  $p=0.02$ ).

#### *Correlations*

No significant correlations were found between changes in exercise blood lactate content or exercise RPE and changes in HR responses to exercise ( $p>0.05$ , see Table 3), although a trend for a correlation ( $r=0.38$ ,  $p=0.07$ ) was found between change in exercise blood lactate content and change in exercise HR.

#### *General linear model analyses*

When examining relations between changes in exercise-onset 20-second and 60-second HR, and HR recovery after exercise (independent variables), in the control vs. intervention group (dependent variable), but with correction for changes in exercise blood lactate content (covariate), no significant relations could be observed ( $p>0.05$ ).

## **Discussion**

No improvement in heart rate (HR) changes during exercise as result of six months of exercise training in patients with multiple sclerosis (MS) was found, despite significant improvements in exercise tolerance. These data thus indicate a negative impact of long-term exercise training on cardiac

autonomic control during exercise in patients with MS. Moreover, correlations between changes in exercise tolerance and changes in HR responses to exercise were absent.

In animal studies and in healthy subjects, improvements in cardiac autonomic control during exercise as result of exercise intervention has been noted repeatedly.<sup>8-10</sup> These improvements can clinically be observed during exercise testing by a lowered resting HR and exercise HR at the same absolute workload, and/or faster HR recovery within one minute after exercise. It is currently believed that these beneficial changes as result of exercise training could, at least in part, be explained by altered activity and/or neural structural changes of the rostral ventrolateral medulla, nucleus tractus solitarii and/or paraventricular nucleus of the hypothalamus,<sup>8,9</sup> although more research seems warranted to fully elucidate these complex mechanisms and/or discover additional pathways. It has, for example, also been proposed that baroreceptor sensitivity and neural reflex activity from skeletal muscle is altered, and sympathetic neural outflow to the sino-atrial node of the heart is reduced, as result of exercise intervention.<sup>8</sup>

In the present study resting HR, 20- and 60-second exercise-onset HR increase, and HR recovery after exercise was not affected by a 24-week exercise intervention in subjects with MS. These data indicate that resting vagal tone, vagal tone withdrawal and/or sympathetic tone activation at initiation of exercise, and parasympathetic tone re-activation after exercise, remains unaltered despite participation into a long-term exercise intervention. Determining the exact etiology of a lack of improvement in cardiac autonomic control in MS remains difficult. The regulation of cardiac autonomic control, and impact of exercise intervention, is complex and remains to be established. However, it can be speculated that vagal nerve activity is disturbed due to brainstem lesions, which is commonly observed in MS, leading to elevated resting HR.<sup>18</sup> Moreover, central command brain structures (primary motor cortex, hypothalamic and subthalamic locomotor regions, mesencephalic locomotor region, selected portions of pons, medulla, but also amygdale) do often suffer from lesions in MS. This central command is responsible for the anticipation to initiation of exercise, as well as resetting baroreflex thresholds, thus regulating early cardiovascular adaptations to exercise (reductions in vagal tone) but in

part also HR during exercise at a later timeframe.<sup>16</sup> It has indeed been shown that the degree of mainly midbrain lesions are correlated with degree of disturbed cardiovascular autonomic control in patients with MS.<sup>19</sup> Based on our data, it thus seems that mainly a persistent dysfunction in the parasympathetic nervous system is present in patients with MS. However, other mechanisms do seem to further contribute to disturbances in cardiac autonomic control during exercise in MS. For example, baroreflex dysfunction has been discovered in patients with MS, thus giving way to disturbed HR responses to exercise.<sup>20</sup> It is important to mention that the above-mentioned brain lesions are often permanent. This might explain why cardiac autonomic dysfunction might persist, even after participation into a long-term exercise intervention, in patients with MS. In final, it could be hypothesized that the volume of exercise would be insufficient to alter autonomic cardiac control during exercise in the studied patients. However, it is difficult to immediately implement high-volume exercise interventions in patients with MS who suffer from limited mobility, neurologic symptoms, and exercise intolerance.

One study previously investigated the impact of exercise intervention on cardiac autonomic control during exercise in MS patients.<sup>11</sup> They concluded that cardiac autonomic control during exercise in MS patients improved because of a less steep HR increase in the final training session (after a 12-week exercise intervention) vs. first training session.<sup>11</sup> However, some patients were on HR-altering medication, HR measurements were executed during training sessions on mechanically-braked bikes in which the cycling load depended on pedaling frequency (thus timing of HR measurement and different cycling frequency/load could have affected the results), HR recovery after exercise was not assessed, and HR was assessed every two minutes (thus being unable to assess early exercise-onset HR changes). Therefore, a study investigating the impact of exercise intervention on cardiac autonomic control during exercise in MS patients remained mandatory, but with standardization of HR measurements and more detailed HR recordings.

It might be argued that a lack of improvement in cardiac autonomic control during exercise in MS patients might be due to the application of an intervention with insufficient impact on human physiology.

However, according to data from the present study the applied exercise intervention was effective to improve exercise tolerance in patients with MS. Significant group\*time interaction effects were found for changes in blood lactate content and Borg ratings of perceived exertion during exercise at similar absolute workload. However, we should remain cautious when concluding that exercise tolerance was significantly enhanced in the intervention group since only changes in blood lactate content and ratings of perceived exertion during exercise were measured. Moreover, although some data indicated an improvement in exercise tolerance as result of exercise training, maybe the applied exercise intensity was not high enough to elicit improvements in cardiac autonomic control during exercise as well. In the present study, low-to-moderate exercise intensities were applied to maximize the feasibility and medical safety of exercise training in patients with MS. It thus remains to be explored whether exercise training could lead to improved cardiac autonomic control during exercise in patients with MS, but with a different selection of training modalities (especially higher training intensities). Nonetheless, it seems fair to conclude that patients with MS are capable of improving their exercise tolerance as result of exercise training despite the presence of such disturbed cardiac autonomic control.

Interferon therapy was significantly related to a greater increase in HR during the first 60 seconds of exercise during follow-up, and a lack of a decrease in exercise blood lactate content. These data might indicate that interferon therapy accelerates tachycardia during the first minute of exercise (which points to an increased sympathetic activation) and inhibits improvements in exercise tolerance. This speculation is in agreement with previous study: chronic interferon therapy leads to a decrease in HR variability (probably due to the development of a hyper-adrenergic state)<sup>21</sup> and reduction in exercise capacity in patients with chronic hepatitis.<sup>22</sup> The reduction in exercise tolerance as result of interferon therapy might result from peripheral vascular endothelial dysfunction.<sup>23</sup>

This study is limited by a relatively small sample size. However, this is the first study that examines the impact of exercise intervention on cardiac autonomic control during exercise in patients with MS with standardized and detailed HR recordings, hereby contributing to greater insights in (causes for) exercise intolerance in MS patients and effects of exercise intervention. Moreover, HR changes to



exercise during follow-up were so small that probably hundreds of subjects with MS must be included in future studies to be able to show significant changes in cardiac autonomic control during exercise. In studies with similar samples sizes, but healthy individuals, long-term exercise intervention did improve cardiac autonomic control.<sup>8,16</sup> As a result, it seems unlikely that a lack of change in cardiac autonomic control during exercise in the present study was mainly due to a small study sample size. It might be argued that in the intervention group, the 24-week exercise test (which was executed on identical absolute workload) was of a relative lower intensity because of an improvement in exercise tolerance in this group. Therefore, sympathetic activation/vagal tone withdrawal might have been less during follow-up assessment in this group, hereby affecting our results. However, according to general linear model analyses changes in exercise blood lactate content during follow-up (which provides an estimate of changes in relative exercise intensity during follow-up testing) did not affect changes in exercise-onset 20-second and 60-second HR, and HR recovery after exercise, during follow-up in total group. In final, this study lacked RR variability assessment: future studies should incorporate such measurement to evaluate the impact of exercise intervention on cardiac autonomic control during exercise in patients with MS.

In conclusion, in MS patients a long-term exercise intervention does not seem to improve HR changes during exercise, despite improvements in exercise tolerance. These data might indicate that cardiac autonomic control during exercise is not easily improved by long-term exercise intervention in patients with MS.

## References

1. Senaratne MPJ, Carroll D, Warren KG, Kappagoda T. Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. *J Neurol Neurosurg Psychiatr* 1984;47:947-52.
2. Flachenecker P, Wolf A, Krauser M, Hartung HP, Reiners K. Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic intolerance. *J Neurol* 1999;246:578-86.
3. Acevedo AR, Nava C, Arriada N, Violante A, Corona T. Cardiovascular dysfunction in multiple sclerosis. *Acta Neurol Scand* 2000;101:85-8.
4. Gunal DI, Afsar N, Tanridag T, Aktan S. Autonomic dysfunction in multiple sclerosis: correlation with disease-related parameters. *Eur Neurol* 2002;48:1-5.
5. Hansen D, Wens I, Dendale P, Eijnde BO. Exercise-onset heart rate increase is slowed in multiple sclerosis patients: does a disturbed cardiac autonomic control affect exercise tolerance? *Neurorehabilitation* 2013;33:139-46.
6. Goldsmith RL, Bloomfield DM, Rosenwinkel ET. Exercise and autonomic function. *Coronary Artery Dis* 2000;11:129-35.
7. Kasahara Y, Izawa K, Omiya K, Osada N, Watanabe S, Saitoh M, et al. Influence of autonomic nervous dysfunction characterizing effect of diabetes mellitus on heart rate response and exercise capacity in patients undergoing cardiac rehabilitation for acute myocardial infarction. *Circ J* 2006;70:1017-25.
8. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. *Sports Med* 2003;33:33-46.
9. Michelini LC, Stern JE. Exercise-induced neuronal plasticity in central autonomic networks: role in cardiovascular control. *Exp Physiol* 2009;94:947-60.

10. Martins-Pinge MC. Cardiovascular and autonomic modulation of the central nervous system after aerobic exercise training. *Braz J Med Biol Res* 2011;44:848-54.
11. Feltham MG, Collett J, Izadi H, Wade DT, Morris MG, Meaney AJ, et al. Cardiovascular adaptation in people with multiple sclerosis following a twelve week exercise programme suggest deconditioning rather than autonomic dysfunction. *Eur J Phys Rehabil Med* 2013;e-pub ahead of print.
12. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983;33:1444-52.
13. Baldari C, Bonavolonta V, Emerenziani GP, Gallotta MC, Silva AJ, Guidetti L. Accuracy, reliability, linearity of Accutrend and Lactate Pro versus EBIO plus analyzer. *Eur J Appl Physiol* 2009;107:105-11.
14. Hansen D, Wens I, Kosten L, Verboven K, Eijnde BO. Slowed exercise-onset VO<sub>2</sub> kinetics during submaximal endurance exercise in subjects with multiple sclerosis. *Neurorehabil Neural Repair* 2013;27:87-95.
15. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985;131:700-8.
16. Seals DR. The autonomic nervous system. In: *ACSM's advanced exercise physiology*, Lippincott Williams & Wilkins, Philadelphia, USA, 2006, p. 197-245.
17. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;352:1951-8.
18. Lu Z, Zhang B, Qiu W, Kang Z, Shen L, Long Y, et al. Comparative brain stem lesions on MRI of acute disseminated encephalomyelitis, neuromyelitis optica, and multiple sclerosis. *Plos One* 2011;6:e22766.
19. Saari A, Tolonen U, Paakko E, Suominen K, Pyhtinen J, Sotaniemi K, et al. Cardiovascular autonomic dysfunction correlates with brain MRI lesion load in MS. *Clin Neurophysiol* 2004;115:1473-8.

20. Sanya EO, Tutaj M, Brown CM, Goel CM, Neundorfer B, Hilz MJ. Abnormal heart rate and blood pressure responses to baroreflex stimulation in multiple sclerosis patients. *Clin Auton Res* 2005;15:213-8.
21. Yamamoto T, Tsuchihashi T, Hayashi J, Kashiwagi S. Effect of interferon therapy on heart rate and sympathetic nervous system. *Fukuoka Igaku Zasshi* 1998;89:207-15.
22. Takase B, Hamabe A, Uehata A, Fujioka T, Kondo T, Matsui T, et al. Recombinant interferon alpha treatment decreases heart rate variability indices and impairs exercise tolerance in patients with chronic hepatitis. *Biomed Pharmacother* 2005;59:S163-8.
23. Takase B, Uehata A, Fujioka T, Kondo T, Nishioka T, Isojima K, et al. Endothelial dysfunction and decreased exercise tolerance in interferon-alpha therapy in chronic hepatitis C: relation between exercise hyperemia and endothelial dysfunction. *Clin Cardiol* 2001;24:286-90.



Table 1. Subject characteristics

|   | control subjects (n=9) | intervention subjects (n=14) |
|---|------------------------|------------------------------|
| age (years)                                     | 46 ± 10                | 50 ± 7                       |
| gender (n male)                                 | 4                      | 4                            |
| body height (m)                                 | 1.71 ± 0.07            | 1.68 ± 0.08                  |
| body weight (kg)                                | 70 ± 10                | 71 ± 18                      |
| body mass index (kg/m <sup>2</sup> )            | 24.2 ± 2.6             | 24.8 ± 5.3                   |
| EDSS  | 3.1 ± 1.4              | 3.2 ± 1.5                    |
| MS type   |                        |                              |
| RRMS (n)  | 6                      | 9                            |
| PPMS (n)  | 2                      | 1                            |
| SPMS (n)  | 0                      | 4                            |
| RPMS (n)  | 1                      | 0                            |
| disease duration (years)                        | 8 ± 6                  | 11 ± 8                       |
| cycling power output<br>during exercise test(W) | 42 ± 12                | 38 ± 10                      |

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; RPMS, progressive relapsing multiple sclerosis.

Table 2. Heart rate responses to exercise and exercise tolerance

|                                    | Start of follow-up |                       | T Six months of follow-up     |                       | time*group interaction |                       | p-value |
|------------------------------------|--------------------|-----------------------|-------------------------------|-----------------------|------------------------|-----------------------|---------|
|                                    | control subjects   | intervention subjects | control subjects <sup>#</sup> | intervention subjects | control subjects       | intervention subjects |         |
| resting heart rate (bts/min)       | 80 ± 13            | 79 ± 13               | 81.3 ± 15.8                   | 77.7 ± 10.9           | 81 ± 17                | 77 ± 8                | 0.61    |
| resting expiratory volume (l/min)  | 10 ± 2             | 9 ± 3                 | 7.7 ± 2                       | 8.8 ± 3.2             | 11 ± 4                 | 10 ± 4                | 0.69    |
| resting blood lactate (mmol/l)     | 2.4 ± 0.7          | 2.7 ± 0.4             | 2.9 ± 0.7                     | 2.3 ± 0.5             | 2.2 ± 0.6              | 2.0 ± 0.6*            | 0.21    |
| resting oxygen uptake (ml/min)     | 229 ± 64           | 273 ± 90              | 240 ± 55                      | 282 ± 94              | 290 ± 60               | 286 ± 91              | 0.34    |
| exercise heart rate (bts/min)      | 107 ± 18           | 108 ± 15              | 107 ± 16                      | 101 ± 9               | 110 ± 17               | 102 ± 9               | 0.13    |
| exercise expiratory volume (l/min) | 28 ± 8             | 24 ± 7                | 24 ± 5                        | 23 ± 7                | 27 ± 6                 | 24 ± 8                | 0.82    |
| exercise blood lactate (mmol/l)    | 3.1 ± 0.5          | 3.1 ± 0.9             | 3.7 ± 0.9                     | 2.6 ± 0.7             | 3.3 ± 1.1              | 2.4 ± 0.7*            | 0.02    |
| exercise oxygen uptake (ml/min)    | 980 ± 274          | 910 ± 253             | 898 ± 161                     | 918 ± 238             | 970 ± 214              | 874 ± 200             | 0.58    |

|   |            |            |            |            |            |            |      |
|---|------------|------------|------------|------------|------------|------------|------|
| exercise rating of perceived exertion               | 10.4 ± 2.3 | 11.6 ± 1.8 | 11.3 ± 2.7 | 10.2 ± 1.9 | 10.6 ± 1.7 | 9.7 ± 2.0* | 0.02 |
| heart rate at 20 seconds of exercise (bts/min)      | 92 ± 16    | 95 ± 13    | 95 ± 16    | 96 ± 14    | 92 ± 17    | 91 ± 9     | 0.34 |
| heart rate change in 20 seconds (bts/min)           | 12 ± 5     | 15 ± 6     | 14 ± 7     | 18 ± 12    | 11 ± 6     | 13 ± 5     | 0.56 |
| heart rate at 60 seconds of exercise (bts/min)      | 100 ± 16   | 101 ± 12   | 102 ± 14   | 99 ± 9     | 101 ± 15   | 99 ± 7     | 0.47 |
| heart rate change in 60 seconds (bts/min)           | 20 ± 7     | 21 ± 8     | 21 ± 8     | 22 ± 5     | 20 ± 6     | 22 ± 6     | 0.89 |
| heart rate at 1 minute of recovery (bts/min)        | 87 ± 18    | 87 ± 16    | 92 ± 21    | 83 ± 10    | 91 ± 18    | 82 ± 9     | 0.13 |
| heart rate change at 1 minute of recovery (bts/min) | 20 ± 8     | 21 ± 8     | 15 ± 9     | 18 ± 10    | 19 ± 3     | 20 ± 6     | 0.73 |

Data are expressed as means±SD.

\*significant change within group (p<0.05)

#Data from three subjects were missing due to illness at time of assessment.



Table 3. Correlations in total group (n=23)

| change in   | change in<br>ratings of perceived exertion<br>during exercise | blood lactate content<br>during exercise |
|---|---|--|
| resting heart rate (bts/min)                        | -0.06   | 0.13                                     |
| exercise heart rate (bts/min)                       | 0.17  | 0.38                                     |
| heart rate at 20 seconds of exercise (bts/min)      | 0.11  | 0.14                                     |
| heart rate change in 20 seconds (bts/min)           | 0.25  | -0.01                                    |
| heart rate at 60 seconds of exercise (bts/min)      | 0.09  | 0.17                                     |
| heart rate change in 60 seconds (bts/min)           | 0.23  | 0.02                                     |
| heart rate at 1 minute of recovery (bts/min)        | 0.13  | 0.33                                     |
| heart rate change at 1 minute of recovery (bts/min) | -0.02   | 0.01                                     |

Correlation coefficients are presented.

Figure 1. Study flowchart

