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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN

master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Impact of a maximal endurance test on perceived symptoms and walking capacity in persons with multiple sclerosis

Promotor :
Prof. dr. Peter FEYS

Copromotor :
De heer Florian VAN HALEWYCK

Lore Vanschoenwinkel

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

Universiteit Hasselt | Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Universiteit Hasselt | Campus Diepenbeek | Agoralaan Gebouw D | BE-3590 Diepenbeek

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MS RUN Project

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I would like to thank all the people who contributed in some way to the work described in this master thesis. First and foremost, I would like to thank my promotor Prof. Dr. P. Feys for the allocation of an interesting topic and for his advice and guidance through the whole process. Without his support I would not have been able to complete this research. Secondly, I would like to thank my co-promotor Dr. F. Van Halewyck, who supported and guided me during every step of the process. Additionally, I take this opportunity to express gratitude to all of the researchers at the Rehabilitation Research Center (REVAL) from the University of Hasselt for their help and support. I am also grateful to my parents, sisters and partner who supported me through this venture.

Broekstraat 71, 3840 Borgloon, 10/06/2015 L.V.

Framework

The current study focuses on the effect of a maximal endurance test on perceived symptoms and walking capacity in Multiple Sclerosis (MS), and may consequently be seen as a contribution to the neurological rehabilitation research domain. This research is of importance for persons with Multiple Sclerosis (pwMS), who seem to benefit from physical activity, but are often limited to be physically active due to the well-known intensification of perceived symptoms.

The study is part of the MS RUN project, that is led by Prof. Dr. Peter Feys and Dr. Florian Van Halewyck in collaboration with Prof. Dr. B. Op ‘t Eijnde and Dr. I. Wens. The MS RUN project was funded by P. Van Asch, the president of Move To Sport (www.movetosport.be), an organization that promotes physical activity in pwMS. In this project, the effect of a 12 week running program on cognitive and motor functioning as well as neuroplasticity is investigated in pwMS. Participants trained during 12 weeks at a submaximal level via personalized training programs, with an intensity that increased gradually until participants were capable of running five kilometers. Before and after the rehabilitation program, pwMS underwent physical and cognitive tests and an MRI scan of the brain.

The current part of the project focuses on the baseline measurements as data collection of the post-intervention measures is still ongoing.

Data collection took place at REVAL in Diepenbeek. Participants were recruited via different MS centers in Belgium, via a network of physiotherapists and neurologists and via social media (Facebook and MS Society Flanders). The study was approved by the Medical Ethical Committee of Hasselt University, Belgium, as well as the Ethical Committee of Virga Jesse Hospital, Belgium.

I had a rather small contribution in the design of the larger MS RUN project. However, during data collection, I was part of the team that instructed and guided the participants through the tests and training. Another responsibility was to construct a user manual for the Withings activity monitor that participants wore during the whole project, resolve technical problems with this activity monitor and observe their physical activity pattern. Also regarding data collection, I consistently accompanied all participants in the University Hospital of Antwerp (Belgium) during their MRI scans. Furthermore, I contributed to the data analysis and interpretation (descriptive data, distance covered during the 6-Minute Walk Test (6MWT), Visual Analogue Scale (VAS) for symptoms, Borg Ratings of Perceived Exertion (RPE) and Timed Chair Stand (TCS)). I performed the academic writing primarily independent, although Prof. Dr. Feys and Dr. F. Van Halewyck provided feedback on several occasions.

Impact of a maximal endurance test on perceived symptoms and walking capacity in persons with Multiple Sclerosis

L. Vanschoenwinkel, F. Van Halewyck, P. Feys

Abstract

Background: Previous studies have indicated that temporary symptoms may occur in persons with Multiple Sclerosis (pwMS) while performing intensive physical activity.

Objective: This study aimed to evaluate the impact of a maximal endurance test and recovery, on perceived symptoms and walking capacity in pwMS.

Methods: Forty-two pwMS reported on the perceived severity of ten symptoms or dysfunctions (fatigue, sensory impairments, balance, etc) by means of the Visual Analogue Scale (VAS) and repeatedly performed a 6-Minute Walk Test (6MWT), before and twice after a maximal endurance test.

Results: Perceived intensity of symptoms increased significantly immediately after the maximal endurance test ($p<0.0001$), but normalized already after a 15 and 60-minute recovery period. PwMS ranked general fatigue as highest (mean = 4.5 ± 2.3), followed by muscle fatigue (mean = 3.6 ± 2.3). Interestingly, there was no significant difference between the distance covered during the 6MWT before (mean = 575 ± 63m) and 15 minutes after (mean = 577 ± 65m) the maximal endurance test.

Conclusion: Perceived intensity of symptoms in pwMS increased significantly after a maximal endurance test, but returned to baseline values after a 15-minute recovery period. A maximal endurance test did not have a significant effect on walking capacity in pwMS.

Keywords

Multiple Sclerosis, physical activity, perceived symptoms, walking capacity, recovery

Introduction

Multiple Sclerosis (MS) is a neurodegenerative disease of the human central nervous system. It is the major cause of non-traumatic neurological disability in young adults. MS is a chronic debilitating disease that reduces lifespan by seven to eight years on average, 50% of persons with Multiple Sclerosis (pwMS) are non-ambulatory 25 years after disease onset[1]. There are two important aspects that have a significant impact on pwMS. First the disease course is variable and unpredictable. Second, a great part of the disease process is silent. Possible symptoms include muscle weakness, extreme fatigue, loss of balance, impaired speech, double vision, declining cognitive function and paralysis[2]. These symptoms clearly result in reduced quality of life. Interestingly, physical activity has been suggested to counteract the disabling symptoms of MS[3-5]. According to Dalgas, even depression can be reduced or prevented by exercise in persons with MS[6]. Also, long term endurance training is known to have beneficial effects on fatigue in pwMS[7-10], increase their maximal oxygen uptake[11] and improve their physical capacity and muscle fitness[12]. Finally, it should be noted that endurance exercise is safe in pwMS when recommended precautions are implemented[13].

Despite these promising benefits of regular physical activity, pwMS seem less physically active than the general population[14-17]. This might be due to physical activity frequently being accompanied by a temporary worsening of symptoms in pwMS that remains insufficiently understood to date. So far, only few studies have investigated the impact of endurance exercise on symptom exacerbation[18-20]. All studies report only a temporary change in symptoms following endurance training, with symptoms returning quickly to baseline levels following a brief recovery period. In a study of Smith[19], for example, one focused specifically on the effects of resistance training and stretching. Subjects were asked to perform exercises at a self-selected intensity they would describe as “somewhat hard” to persevere. Before the exercise session, participants were asked to indicate to what extent they experienced symptoms. Afterwards, patients had to indicate if they experienced any changes in the severity of sensory symptoms using a visual analogue scale (VAS). Monitoring of any further changes in sensory symptoms took place until baseline levels were attained. Effect of physical activity on perceived physical function was evaluated based on self-rated expected degree of difficulty with physical function[19]. Results showed that pwMS experienced a temporary change in sensory symptoms meaning that symptoms returned to pre-exercise levels after thirty minutes to maximally three hours. Changes in sensory symptoms were more likely to occur in people with relatively more symptoms at baseline and in older participants. A single exercise session did not appear to affect fatigue levels or general physical functioning (i.e., ease of walking, eating and dressing) significantly. Another study by Schmidt and colleagues[11] reported that, long-term endurance training had a moderate, but significant effect on fatigue in patients with significant fatigue at baseline. However, the worsening of symptoms following physical activity seemed to be only temporary. All in all, we can conclude that little research has been done about the time needed to recover from these MS-related symptoms and which symptoms are experienced the most.

The aim of this study was therefore to evaluate the impact of a maximal endurance test on perceived symptoms and walking capacity in pwMS. Compared to Smith et al.[19], the intensity of physical activity was higher in our study, since pwMS were instructed to execute a maximal endurance test. The effect on physical functioning in our study (walking capacity in particular), was measured based on three 6-Minute Walk Tests (6MWTs) rather than self-rated questionnaires. In contrast to Smith et al.[19], baseline VAS scores for intensity of symptoms were recorded, to be able to quantify differences before and after the maximal endurance test. We expected an increase in the intensity of symptoms following the maximal endurance test. Despite the fact that, according to Feys et al.[21], general fatigue should not have an effect on walking capacity, we expected that the performance on the 6MWT could be affected by other possible symptoms (e.g., muscle fatigue, balance difficulties, etc.) immediately following the maximal endurance test.

Materials and methods

Participants

We included forty-two pwMS in the study. Descriptive outcome measures can be derived from Table 1. The inclusion criteria for participation were: an EDSS score lower than/equal to 3; being older than 18 years old at the start of the study; being able to walk five kilometers without any aid, (but not yet being able to run five kilometers) prior to the study; not wearing a pacemaker (for MRI scans only) and provided written informed consent. Participants were recruited via different MS centers in Belgium, via a network of physiotherapists and neurologists and via social media (Facebook and MS Society Flanders). The study was approved by the Medical Ethical Committee of Hasselt University, Belgium, as well as the Ethical Committee of Virga Jesse Hospital, Belgium.

Study design

This study used a pre-post design to examine the effect of a maximal endurance test, and recovery, on perceived symptoms and walking capacity. Specifically, the testing protocol started with a first 6MWT followed by a maximal endurance test. Fifteen minutes after the endurance test, another 6MWT was performed, as well as one hour after the endurance test. Thus, every participant performed three 6MWTs in total (6MWT 1, 6MWT 2 and 6MWT 3, respectively). This protocol allowed us to determine changes in the functional walking capacity after vigorous physical activity. Before and after the maximal endurance test and every 6MWT, participants were asked to rate their perceived symptoms on a scale from 0 (minimal intensity) to 10 (maximal intensity) in order to assess symptom change and recovery after physical activity. Subsequently, a 5-repetition sit-to-stand test (5STS) was executed before every 6MWT. The study design is shown in Fig. 1.

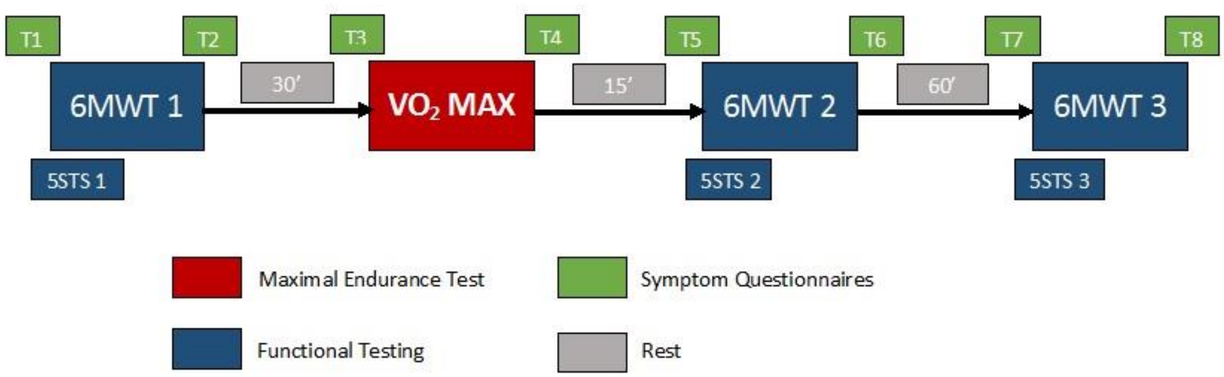

Figure 1. Study design

Abbreviations: 6MWT 1: 6MWT pre maximal endurance test; 6MWT 2: 6MWT 15' post maximal endurance test; 6MWT 3: 6MWT 60' post maximal endurance test; VO_2max: Maximal oxygen uptake during the maximal endurance test; 5STS: 5-repetition sit-to-stand test; T1: pre 6MWT 1; T2: post 6MWT 1; T3: pre maximal endurance test; T4: post maximal endurance test; T5: pre 6MWT 2; T6: post 6MWT 2; T7: pre 6MWT 3; T8: post 6MWT 3
Three 6MWTs were performed, one before the maximal endurance test, and two after a 15 and 60-minute recovery period. Before every 6MWT a 5STS was performed. Immediately before and after the 6MWTs and maximal endurance test, the VAS score for perceived intensity of symptoms was questioned.

Outcome Measures

Descriptive Outcome Measures

Questionnaires. The following questionnaires were collected prior to the tests: Multiple Sclerosis Walking Scale-12 (MSWS-12)[22] with a total score ranging from 12 (no limitation on gait-related activities) to 60 (extreme limitation on gait-related activities) and Fatigue Scale for Motor and Cognitive Functions (FSMC) (subscore motor and cognitive)[23] with a total score ranging from 20 (no fatigue at all) to 100 (severest grade of fatigue).

Experimental Outcome Measures

Perceived symptoms severity. A list of possible MS-related symptoms was developed, based on an existing questionnaire of six symptoms by Skjerbaek and colleagues[18]. The list touched upon general fatigue, muscle fatigue, balance, gait pattern, muscle weakness, spasticity/muscle stiffness, pain, sensory impairments, visual impairments and dizziness. The participants were asked to what degree they were affected by these symptoms and rate the severity of them on a VAS from 0 (minimal intensity) to 10 (maximal intensity). Finally, participants were asked if they experienced any additional symptoms.

6MWT. During the 6MWTs participants were instructed to walk as far as possible in six minutes time. They walked on a 30-m straight line, turning around cones at each end[24]. The distance covered during the 6MWT was registered[25].

Borg Ratings of Perceived Exertion (Borg RPE)[26]. Participants had to rate perceived exertion following the three 6MWTs on a Borg RPE scale (6-20 scale).

5-repetition sit-to-stand test (5STS)[27]. In this test, the participants were asked to cross their arms in front of their chest and place their hands on the opposite shoulder. Then the participants had to stand up and sit down five times as fast as possible from a chair without arm rests. The time needed to perform this simple motor test, is traditionally regarded as a measurement for functional lower limb muscle strength and was used to quantify functional change of transitional movement[27].

Intervention

Participants started the maximal endurance test on a bicycle with a 10-minute warm-up at a resistance level between 30 and 35 watt. The patients were instructed to cycle at their preferred pace, but they had to reach 75 rotations per minute by the end of the warm-up. For women, the maximal endurance test started with a resistance of 20 watt, which was raised with 10 watt every minute. For men the maximal endurance test started with a resistance of 30 watt, which was raised with 15 watt every minute.

During the test, all participants were instructed to cycle at a pace of 75 rotations per minute until exhaustion. Oxygen uptake rate was constantly monitored and heart rate and lactate levels in the blood were measured at the end of every minute via a heart rate monitor around the chest (Polar, Kempele Finland) and by collecting capillary blood samples from the earlobe using a portable lactate analyzer (Accutrend Plus, Roche Diagnostics Limited) [28], respectively. After the maximal endurance test, participants could recover for two minutes. Then, a final heart rate and blood lactate measurement was performed to assess recovery and maximal lactate levels.

Statistics

The effect of the maximal endurance test on perceived symptoms

To examine the effect of the maximal endurance test on perceived intensity of symptoms, a repeated measures analysis of variance (ANOVA) was performed, with additional Tukey HSD post-hoc tests executed when appropriate. Data analyses were performed based on change in VAS-score before (T3) and immediately after (T4) the maximal endurance test. In an attempt to examine the effect of recovery on perceived intensity of symptoms, similar analyses were performed based on change in VAS-score after a 15-minute (T5) and 60-minute (T7) recovery period.

In an additional analysis we investigated the direct impact of the 6MWTs on perceived intensity of symptoms. Another repeated measures ANOVA was therefore performed based on change in VAS-score before and after the three 6MWTs (T1 vs T2; T5 vs T6 and T7 vs T8 for 6MWT 1, 6MWT 2 and 6MWT 3, respectively). Only 2.4% of the VAS-scores was missing, and imputation was used to replace this missing data. To determine reliability of the symptom questionnaire, Intraclass Correlation Coefficient (ICC) of mean VAS scores and VAS scores per sub-question between T1 and T3 was calculated.

The effect of the maximal endurance test on walking capacity

To examine the effect of a maximal endurance test on walking capacity during the 6MWT, a repeated measures ANOVA was performed based on change in distance covered during 6MWT before (6MWT 1) and immediately after (6MWT 2) the maximal endurance test. Afterwards the effect of a maximal endurance test on perceived fatigue (BORG RPE) during the 6MWT was examined based on the same statistical test. Finally, the effect of the maximal endurance test on functional lower limb muscle strength during the 5STS was also examined based on repeated measures ANOVA. Post-hoc Tukey HSD tests were executed when appropriate. All analyses were performed using JMP (SAS, Cary, USA) with the level of significance set at $\alpha < 0.05$.

Results

Table 1 shows descriptive measures for the 42 participants (no drop-outs). A mean score of 20.48 on the MSWS-12 indicates low limitation on gait-related activities, whereas a mean score of 61.88 on the FSMC indicates moderate grade of fatigue. Mean maximal oxygen uptake (VO_2max) and maximal lactate values, measured during the maximal endurance test, were rather poor based on normative data for healthy controls (Table 2).

The ICC of mean VAS scores between T1 and T3 was 0.880, indicating a moderate reliability of the symptom questionnaire. ICC of the separate symptoms questioned were 0.868 for *general fatigue*, 0.811 for *muscle fatigue*, 0.872 for *balance*, 0.778 for *gait pattern*, 0.893 for *muscle weakness*, 0.760 for *spasticity/muscle stiffness*, 0.899 for *pain*, 0.854 for *sensory impairments*, 0.962 for *visual impairments* and 0.709 for *dizziness*. These findings all indicate a moderate to strong reliability of the sub-questions in the symptom questionnaire.

Table 1. Sample Characteristics

Variables	***Mean ± Std dev***
Age (years)	40.50 ± 9.28
Gender M/F (%)	4 (9.5%) /38 (90.5%)
Weight (kg)	71.69 ± 13.34
MSWS-12	20.48 ± 8.40
FSMC	61.88 ± 18.75

Abbreviations. Std dev: Standard deviation; MS: Multiple Sclerosis; PDDS: Patient Determined Disease Steps; MSWS-12: 12-item Multiple Sclerosis Walking Scale; FSMC: Fatigue Scale for Motor and Cognitive Functions; T25FW: Timed 25-Foot Walk

Table 2. Descriptive data maximal endurance test

Variables	***Mean ± Std dev***
VO_2max (ml/min/kg)	22.39 ± 5.01
HR_{max} (bpm)	169.81 ± 15.41
$HR_{recovery}$ (bpm)	124.12 ± 16.55
$Lactate_{max}$ (mg/dl)	7.83 ± 3.04

Abbreviations: Std dev: Standard deviation; VO2max: maximal oxygen uptake; HRmax: Maximum Heart Rate; HRrecovery: Recovery Heart Rate

The effect of the maximal endurance test on perceived symptoms

Perceived intensity of symptoms increased significantly immediately after the maximal endurance test ($p < 0.0001$), indicating a clear effect of maximal endurance test on perceived symptoms. Post-hoc tests revealed that these adverse effects normalized already after a 15 and 60-minutes recovery period ($p = 0.0923$ and $p = 0.9979$ compared to baseline, respectively). Participants did not report any additional symptoms.

In general, MS-related symptoms were perceived the most immediately after the maximal endurance test (mean score at T4 = 3.1 ± 2.9). After a 15-minute recovery period, the mean intensity had generally decreased (mean score at T5 = 2.3 ± 2.3). The mean intensity of symptoms tended to reach baseline levels after a 60-minute recovery period (mean score at T7 = 1.7 ± 2.1 and mean score at T1 = 1.8 ± 2.2: *p = 1.0000)*. Regarding specific symptoms pwMS ranked *general fatigue* as the most affecting symptom (mean score over different timeslots = 4.4 ± 2.4), followed by *muscle fatigue* (mean = 3.6 ± 2.3). Interestingly, *muscle fatigue* was the symptom with the greatest increase in perceived intensity after the maximal endurance test, followed by *general fatigue*. Smaller yet significant increases were also seen in perceived *gait pattern*, *dizziness* and *muscle weakness*. The other symptoms did not change significantly over time, as can be seen in Figure 1. The average difference in the VAS, before compared to after the three 6MWTs was only 0.2, 0.2 and 0.3 respectively. Consequently, there was no significant increase in the perceived intensity of symptoms after a 6MWT. Even after multiple efforts on the same day, there is no effect of a 6MWT on perceived symptoms (p = 0.7906, p = 0.9210 and p = 0.6427 for 6MWT 1, 6MWT 2 and 6MWT 3 respectively).

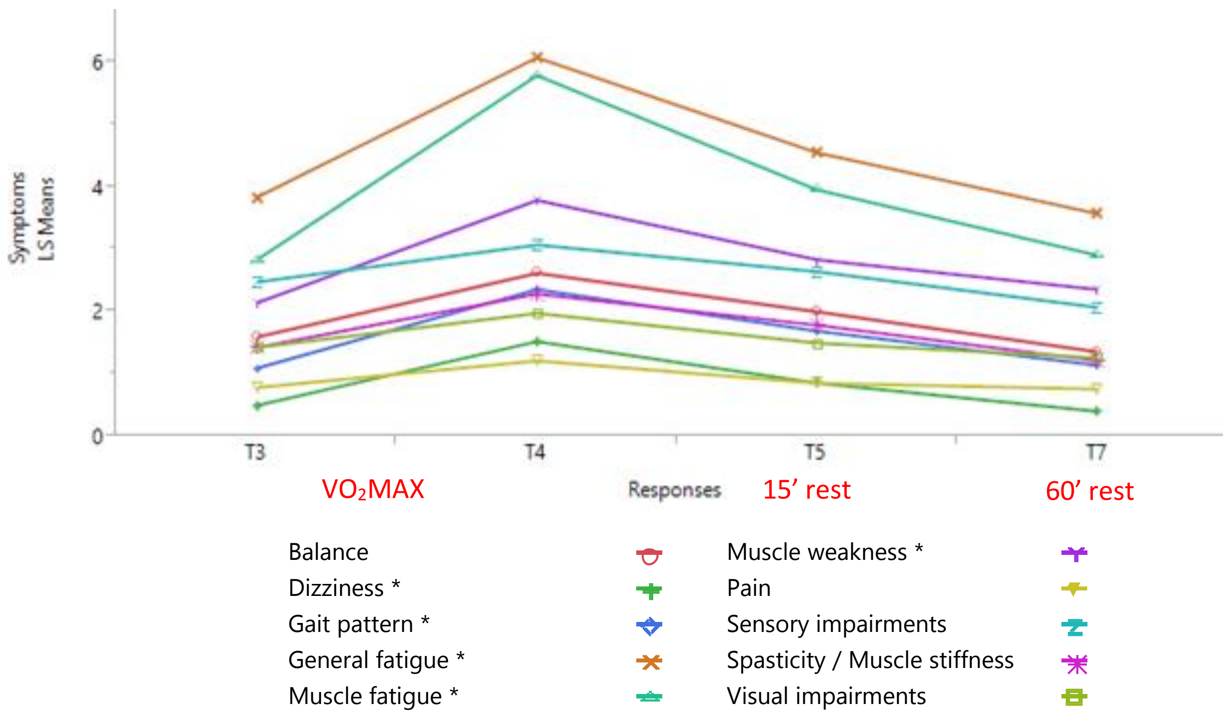

Figure 2. The effect of the maximal endurance test on perceived symptoms. Results are displayed as mean VAS scores per symptom.
* $p < 0.05$ (T3 vs T4)
Perceived intensity of overall symptoms increased significant following the maximal endurance test. These effects normalized after a 15-minute recuperation period. Subscores: significant increases were seen in general fatigue, muscle fatigue, gait pattern, dizziness and muscle weakness.

Table 3. Effect of maximal endurance test and 6MWT on perceived symptoms (VAS)

SYMPTOMS VAS 0-10	***T1***	***T2***	***T3***	***T4***	***T5***	***T6***	***T7***	***T8***	***Mean ± Std Dev [Upper 95% mean - Lower 95% mean]***
General fatigue	3.8 ± 2.3	4.1 ± 2.2	3.8 ± 2.3	6.1 ± 2.5	4.5 ± 2.2	5.0 ± 2.2	3.6 ± 2.3	4.0 ± 2.4	**4.4 ± 2.4 [4.6-4.1]**
Muscle fatigue	2.4 ± 1.9	3.1 ± 2.0	2.8 ± 2.2	5.8 ± 2.5	4.0 ± 2.1	4.4 ± 2.1	2.9 ± 1.9	3.6 ± 2.1	**3.6 ± 2.3 [3.9-3.4]**
Balance	1.7 ± 2.1	1.8 ± 2.1	1.6 ± 2.1	2.6 ± 2.7	2.0 ± 2.3	2.0 ± 2.4	1.4 ± 1.8	1.7± 2.0	**1.8 ± 2.2 [2.1-1.6]**
Gait pattern	0.8 ± 1.2	1.2 ± 1.6	1.1 ± 1.5	2.4 ± 2.2	1.7 ± 1.8	1.9 ± 1.8	1.1 ± 1.5	1.4 ± 1.8	**1.5 ± 1.7 [1.7-1.3]**
Muscle weakness	2.3 ± 2.5	2.5 ± 2.4	2.1 ± 2.3	3.8 ± 2.8	2.8 ± 2.3	3.0 ± 2.3	2.4 ± 2.4	2.4 ± 2.4	**2.7 ± 2.5 [2.9-2.4]**
Spasticity/ muscle stiffness	1.4 ± 1.9	1.6 ± 1.9	1.4 ± 1.6	2.3 ± 2.3	1.8 ± 2.0	2.1 ± 2.1	1.2 ± 1.5	1.4 ± 1.4	**1.7 ± 1.9 [1.9-1.5]**
Pain	1.0 ± 1.8	1.1 ± 1.8	0.8 ± 1.5	1.2 ± 1.6	0.9 ± 1.4	1.1 ± 1.5	0.8 ± 1.3	1.0 ± 1.7	**1.0 ± 1.6 [1.1-0.8]**
Sensory impairments	2.3 ± 2.6	2.5 ± 2.7	2.5 ± 2.7	3.1 ± 2.8	2.6 ± 2.7	2.9 ± 2.9	2.1 ± 2.6	2.3 ± 2.7	**2.5 ± 2.7 [2.9-2.2]**
Visual impairments	1.5 ± 2.2	1.7 ± 2.2	1.4 ± 2.0	2.0 ± 2.5	1.5 ± 2.1	1.5 ± 2.1	1.3 ± 2.0	1.3 ± 2.0	**1.5 ± 2.1 [1.8-1.3]**
Dizziness	0.4 ± 0.8	0.6 ± 1.1	0.5 ± 0.9	1.5 ± 2.0	0.9 ± 1.4	0.8 ± 1.3	0.4 ± 0.8	0.6 ± 1.1	**0.7 ± 1.3 [0.8-0.6]**
Mean ± Std Dev [Upper 95% mean - Lower 95% mean]	**1.8 ± 2.2 [2.0-1.6]**	**2.0 ± 2.3 [2.2-1.8]**	**1.8 ± 2.2 [2.0-1.6]**	**3.1 ± 2.9 [3.3-2.8]**	**2.3 ± 2.3 [2.5-2.0]**	**2.5 ± 2.5 [2.7-2.2]**	**1.7 ± 2.1 [1.9-1.5]**	**2.0 ± 2.3 [2.2-1.8]**	

Abbreviations: Std dev: Standard deviation; T1: pre 6MWT 1; T2: post 6MWT 1; T3: pre maximal endurance test; T4: post maximal endurance test; T5: pre 6MWT 2; T6: post 6MWT 2; T7: pre 6MWT 3; T8: post 6MWT 3

Table 4. Functional Testing

	6MWT 1	*6MWT 2*	*6MWT 3*	*p-value*
Distance	575.1 ± 63.3 [594.9-555.4]	577.5 ± 65.6 [597.9-557.0]	586.5 ± 71.4 [608.7-564.2]	0.7145
Delta VAS	0.2 ± 1.0 [0.3-0.2]	0.2 ± 1.0 [0.3-0.1]	0.3 ± 0.8 [0.4-0.2]	0.4179
BORG RPE	10.2 ± 1.9 [10.8-9.6]	11.3 ± 2.0 [12.0-10.8]	11.1 ± 2.2 [11.8-10.4]	0.0006*

*Significant difference between 6MWT 1 and 6MWT 2

The effect of the maximal endurance test on walking capacity

There was no significant difference between the distance covered during the 6MWT before (mean = 575.1 ± 63.3) and 15 minutes after (mean = 577.5 ± 65.6) the maximal endurance test, indicating no effect of a maximal endurance test on walking capacity in pwMS as shown in table 4. The mean distance covered during 6MWT 3 (mean = 586.5 ± 71.4) even tended to be higher compared to 6MWT 1 and 6MWT 2, but this increase did not reach the level of significance ($p = 0.7179$ and $p = 0.8102$ compared to 6MWT 1 and 6MWT 2, respectively). Also, there was no significant effect of the maximal endurance test on functional lower limb muscle strength based on the 5STS ($p = 0.1844$) (5STS 1 = 10.1 ± 2.4s, 5STS 2 = 9.8 ± 2.2s and 5STS 3 = 9.7 ± 2.2s). The maximal endurance test did have an effect on perceived fatigue during the 6MWT, based on Borg RPE ($p = 0.0006$), which can be seen in table 4.

Discussion

The present study investigated the effect of a maximal endurance test on perceived symptoms and walking capacity in pwMS. A summary and interpretation of our results is provided below. Afterwards, some potential caveats are discussed in the limitations section, followed by a brief conclusion.

The effect of the maximal endurance test on perceived symptoms

A single bout of intense physical activity had a clear and immediate effect on intensity of several perceived symptoms. Specifically, *general fatigue, muscle fatigue, muscle weakness, gait pattern* and *dizziness* increased significantly following the maximal endurance test. However, these adverse effects appeared rather temporary as they normalized already after 15 minutes and reached baseline levels after a 60-minute recovery period. In line with the results of the maximal endurance test, our additional analysis showed that brief bouts of moderate physical activity (i.e. 6MWTs) had no significant effect on the perceived intensity of symptoms in pwMS. These results are largely in line with the literature.

For instance, Smith et al.[19] reported that pwMS with mild to moderate disability experienced a temporary change in sensory symptoms after resistance training and stretching (mean duration of the exercise sessions was 17.4 ± 8.8min). Symptoms returned to pre-exercise levels after 30 minutes to maximally three hours. Interestingly though, perceived levels of fatigue immediately after physical exercise did not differ from pre-exercise levels, just as the levels of fatigue during an additional follow-up 24 hours later. The latter finding is thus in contrast with our study, where *general fatigue* increased the most after the maximal endurance test while no significant changes in sensory impairments were reported by pwMS. A possible explanation for this inconsistency may be that our participants performed a maximal endurance test, which has a higher intensity than the physical exercise in the study of Smith[19].

In another interesting study, Skjerbaek and collegues[18] examined differences in intensity and number of symptoms in heat sensitive pwMS after endurance training and exercise training. Findings were analogous to our study, indicating an increase in perceived intensity of symptoms immediately following the endurance training. These adverse effects normalized after a 60-minute recovery period. Resistance training did not induce symptom exacerbation in heat sensitive pwMS.

According to Dawes et al.[20], pwMS experienced sensations of leg fatigue (BORG CR10-scale) that were comparable to sensations experienced by their healthy controls, immediately following a cycle ergometer incremental exercise test to exhaustion. Both pwMS and their healthy controls ended a maximal exercise test as result of leg muscle fatigue, without difference in the intensity of leg muscle fatigue. In pwMS, though, perceived symptoms were higher after three and five minutes, but there were no differences after ten minutes following physical exercise, indicating pwMS needed more time to recover than their healthy controls[20].

PwMS who participated our study demonstrated only mild to moderate disability level. Total distance covered during the 6MWTs was situated within reference values for healthy subjects form 20-50 years old[29]. This could be an explanation of the minimal effects of the 6MWTs on the perceived intensity of symptoms. Therefore, further research could be useful to draw conclusions for a more heterogeneous group of pwMS.

The effect of the maximal endurance test on walking capacity

The maximal endurance test had no effect on the distance covered during a 6MWT, following recovery periods of 15 and 60 minutes. In line with the findings of Feys and colleagues[21], the abovementioned changes in instant fatigue levels were thus not associated with changes in walking capacity.

According to McLoughlin and colleagues[30], performing a 6MWT had a significant effect on lower limb strength, based on isometric strength tests and postural sway in pwMS. These findings are in contrast with our study, in which functional lower limb strength based on the 5STS, did not significantly differ 15 minutes following the maximal endurance test. However, we should be cautious when making direct comparisons between both studies as intensity of physical exercise and measurements of lower limb strength did not correspond.

Clinical implications

As stated before, pwMS seem to be less physically active than the healthy population. This difference is likely due to the temporary worsening of perceived symptoms following physical activity. This temporary worsening of perceived symptoms after intense physical activity was confirmed by our results. However, the results also highlighted that the adverse effects are only temporary. The absence of long-term symptom exacerbation following physical tests may thus support pwMS to pursue a physically active lifestyle, especially if we consider the benefits that physical activity seems to have in pwMS, such as improved health-related quality of life and decreased levels of fatigue in pwMS[7-10, 12, 31]. Finally, our results further emphasize that a maximal endurance test can be performed in pwMS and causes only limited, temporary symptoms.

Study limitations

It should be noted that the findings of this study only apply to pwMS with limited physical impairments (EDSS < 3), and may not apply to pwMS unable to walk 5km without aid. More than 90% of the participants were women, indicating no equal distribution of sexes. Further research is thus needed to draw conclusions for a more heterogeneous group of pwMS. For the sake of completeness, it would have been interesting to question the perceived intensity of symptoms by telephone 24 hours following physical activity, as some participants verbally reported an increase in perceived fatigue the following day. Further research may thus focus on the delayed effects of intensive physical activity on symptom exacerbation in pwMS. Finally, it would have been recommended to execute the 5STS before and after the maximal endurance test and three 6MWTs, in order to get a better view of the effect of the maximal endurance test and 6MWT on functional lower limb strength.

Conclusion

Perceived intensity of symptoms in pwMS generally increased after a maximal endurance test, but quickly returned to baseline values after a 15-minute recovery period. After a 60-minute recovery period, the perceived severity of symptoms had returned to baseline values completely. Also, a maximal endurance test did not appear to have a significant effect on walking capacity in pwMS, as measured by the distance covered in a 6MWT. The results of this study highlight the lack of long-term adverse effects of physical activity on perceived intensity of symptoms, highlighting that pwMS are able to enjoy physical exercise without long-term symptom exacerbation.

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