2013•2014
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Objective assessment of neuromuscular fatigue in patients with multiple sclerosis

Promotor :
Prof. dr. Peter FEYS

Copromotor :
Mevrouw Deborah SEVERIJNS

Eline Swinnen

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

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KNOWLEDGE IN ACTION

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Acknowledgments

I am Eline Swinnen, a master student in the rehabilitation science and physiotherapy at the university of Hasselt. I would like to say thanks to everyone who helped and supported me, so I could complete my thesis and could generate this result.

A special word of thanks to my promotor prof. dr. P. Feys and to PhD student D. Severijns, to guide me in the neurological research domain, to share their knowledge and to help me to succeed in this research.
I want to thank all the test subjects for their voluntary cooperation, pleasant enthusiasm and spent time.
I would also say thanks to the Revalidatie en MS centrum Overpelt for their comfortable cooperation and to give me permission to work together with the patients and their caregivers.

Finally, I would like to thank my dear family, friends and fellow students for their ever-present support and assistance throughout my five years education to become a rehabilitation and physical therapist.

Lozen, 11 May 2014 S.E.

Research framework

The study 'Objective assessment of neuromuscular fatigue in patients with multiple sclerosis' belongs to the research domain of neurological revalidation: applied research.
Patients with multiple sclerosis (MS) often report, in addition to loss of strength and spasticity, excessive fatigue. This fatigue may have an impact on performing activities of daily living (1). Yet, it is not known how to document objectively the perceived fatigue. It is only expressed subjectively, by means of standardized fatigue questionnaires.
To decide if neuromuscular fatigue is present in patients affected by MS, it seems to be important to have a cut-off score or a standard procedure to define neuromuscular fatigue. It seems useful to have a standard protocol to assess the degree of presence of exercise-induced neuromuscular fatigue.
Methods to objectively measure neuromuscular fatigue could provide more knowledge about patients with MS and it might be helpful in planning the rehabilitation program.

This study is a part of an on-going doctoral project of PhD student D. Severijns, entitled 'Motor fatigue during upper and lower extremity function in multiple sclerosis'.
The research question was designed by the student in consideration with the promotor. The student helped in the recruitment of patients with MS and healthy controls. The protocol was already applied in patients with MS in the pilot study of Jasper Grevendonck (Msc student in AJ 2012-13). The data-acquisition and data-analysis was done by Eline Swinnen (master student rehabilitation science and physiotherapy), in collaboration with PhD student D. Severijns and Falke Bogaerts (master student biomedical science). Writing this master thesis was done by Eline Swinnen, guided by prof. dr. P. Feys (promotor) and PhD student D. Severijns.

This research took place in REVAL, UHasselt Campus Diepenbeek, Agoralaan gebouw A, and the Revalidatie & MS centrum Overpelt.
The purpose was to investigate (1) if this exercise protocol can provoke and detect objectively and subjectively neuromuscular fatigue in patients with MS, if recovery occurs after a rest period, and if neuromuscular fatigue is more prominent in patients with MS as compared with healthy subjects, (2) the psychometric properties of the hand grip force measurement and the fatigue indices.

Objective assessment of neuromuscular fatigue in patients with multiple sclerosis

Objective assessment of neuromuscular fatigue in patients with multiple sclerosis

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Abstract

Background: Patients with multiple sclerosis (MS) often experience fatigue. It is not clear how to document the neuromuscular fatigue using a standard procedure with a defined cut-off score. To be able to interpret the score correctly, one has to know the reliability of the indices and the error of measurement.

Objective: To determine objectively and subjectively the occurrence of neuromuscular fatigue in multiple sclerosis patients while performing a hand grip exercise protocol. Secondly, to investigate the psychometric properties of the hand grip force and fatigue indices.

Methods: Twenty patients with multiple sclerosis and 20 age and sex-matched healthy controls were studied on three test days, using isometric grip force tests. Participants had to perform exercises by hand grip contractions. Important outcome measures were maximal strength, fatigue indices and subjective experience of fatigue, recorded at maximal five test moments per day. The grip force was measured by a hand held e-link dynamometer. The arm function was assessed by questionnaires (Neurological Fatigue Index for Multiple Sclerosis, Modified Fatigue Impact Scale) and clinical tests (Motricity Index, Modified Ashworth Scale, Box and Block Test).

Results: The maximal grip force in the hand which performed the exercises decreased significantly over time in both the healthy controls and patients with multiple sclerosis with similar magnitude. However, the patients with multiple sclerosis showed more neuromuscular fatigue during a sustained force measurement, in comparison with healthy controls ($p<0,05$). The intraclass correlation coefficient showed, for both healthy controls and patients with multiple sclerosis, a good reliability for the maximal hand grip strength and a poor to moderate reliability for the static and dynamic fatigue indices.

Conclusion: The applied protocol of performing exercises by hand grip contractions could elicit neuromuscular fatigue in both the dominant and non-dominant hand of healthy controls and patients with multiple sclerosis. The grip strength and fatigue indices are considered as reliable.

Keywords

multiple sclerosis, upper extremity, neuromuscular fatigue, assessment

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system. It is characterized by inflammation, gliosis, demyelination and destruction of axons and neurons (2). Spasticity, loss of strength and fatigue are symptoms which patients with MS often experience. Activities of daily living may be affected by the experienced fatigue (1).
Fatigue can be defined as the awareness of a reduced capacity to produce physical or mental activity (3). Physical fatigue is associated with muscular effort, whereas mental fatigue appears during cognitive tasks (4). Neuromuscular fatigue is a subcategory of 'physical fatigue'. Neuromuscular fatigue is a reduced capacity of the neuromuscular system in creating a maximal force following prolonged or sustained muscle activity (5).

Characterizing and measuring fatigue is difficult to do (3), probably related to the vagueness of the term 'fatigue' and the inherent problems with fatigue assessment. Different subjective tests are used to measure fatigue in patients with MS (6;7). There is no general consensus on how to document objectively the perceived neuromuscular fatigue. Several protocols and outcome measures are described in literature (8;9). Protocols to measure neuromuscular fatigue included static sub-maximal and maximal force contractions, 30-second sustained isometric contractions, a series of brief maximal dynamic contractions and the measurement of recovery time (9-11). Previous reports on muscle fatigue in persons with central nervous system disorders have used different outcome measures such as: electromyography (EMG) and force (8;12). Neuromuscular fatigue can be quantified as the decline in power, speed or accuracy after performing an exercise intervention (13). According to Dobkin, neuromuscular fatigue can be assessed by means of a comparison of maximal voluntary contractions (MVC) before and after an exercise protocol (12), but according to our knowledge, studies has not been previously reported. However, not only the maximal contraction is important, also the ability to sustain repeated contractions is important because various activities of daily living require repetitive contractions of variable intensity (14). This is often trained by means of repeated exercises. Persons with MS often report fatigue during physical exercise, and fatigue is a factor which can impede participation in exercise (15). Often, technology assisted training is used, in order to improve compliance with exercise.

Patients with MS are often weak in lower extremity muscles (16). Although strength in the upper extremity of patients with MS is relatively preserved in the early stage of the disease, 76% of the patients with MS experienced a mild disability in hand function. Upper limb rehabilitation is gaining more interest, since any upper limb dysfunction is impacting on activities of daily living (17). Key elements in arm-hand function are reaching, grasping and in-hand manipulation (18). Furthermore, hand grip force is often considered to be a possible predictor of overall body strength (19). Healthy people use their hands continuously in activities of daily living, like washing, dressing, eating and working. Efficient regulation of the grip force and correct somatosensory information are essential in performing daily life activities (18;20). This already seems to be impaired in persons with MS (21). It is important to split up the hands in a dominant and non-dominant hand. The hand subjects prefer to use

in activities of daily living is the dominant hand (22). Grip force is expected to be 10% higher in the dominant hand as compared with the non-dominant hand (23). Neuromuscular fatigue could be expected to be higher in the non-dominant hand, the hand which is less used during the day. A hypothesis is that neuromuscular fatigue is more present in patients affected by MS, as compared with healthy subjects, because of the changes in the nervous system and the influence on the upper extremities. More knowledge about neuromuscular fatigue in patients with MS and the perceived fatigue, might be helpful in the creation of the most optimal assessment and tailored rehabilitation program.

The aim of the present study was 1) to examine objectively and subjectively if neuromuscular fatigue and recovery occur during an exercise protocol for hand grip strength, and to examine if it is more prominent in patients with MS, compared with healthy subjects, and 2) to explore the reliability of the measurements to estimate the extent to which the measurements were consistent and free from error.

Methods

Participants

A total of 20 patients affected by MS (7 men, 13 women) were recruited in the Revalidatie & MS centrum Overpelt. MS patients were included in the study if they fulfilled following inclusion criteria: (1) a definite diagnosis of MS according to the Mc Donald criteria (24), (2) 18 years or older and (3) the ability to perform voluntary movements in both arms and hands. Patients were excluded if: (1) a relapse occur or being under relapse-related corticoid treatment, one month prior to the study, (2) having cardiovascular or orthopaedic disorders, (3) cognitive limitations, which impair the ability for patients to adhere to instructions or to sign informed consent conscious and (4) having excessive spasticity (Modified Ashworth Scale (MAS) > 2). Twenty gender and age-matched healthy controls were included in the study. Informed consent was obtained from each participating subject. Study approval was granted by the medical ethical committee of University Hospitals in Leuven, University of Hasselt and RMSC Overpelt in February 2013.

Study procedure

The study was a cross-sectional study. Experimental outcome measures were assessed during three sessions, each lasting maximum 90 minutes. Between each visit, there were minimum 24 hours of rest, to avoid influences of one test day on another. The first test day involved the collection of descriptive data of the participating subjects and the variability of maximal hand grip strength measures was examined. The between day variability was based on the maximal grip strength measures and the fatigue indices. The intraclass correlation coefficient (ICC) was determined for both the maximal hand grip strength, the sustained fatigue index (SFI) and the dynamic fatigue index (DFI). The ICC ranges between 0,00 and 1,00. To assess the reliability in this study a guideline was used, which suggests that values below 0,50 are indicative of poor reliability, those between 0,50 and 0,75 of moderate reliability and those above 0,75 of good reliability (25).

The standard error of measurement (SEM) for the variables measured at test moment one (T1) of each test day, was determined using the formula

$$SEM = SD \sqrt{(1 - r_{xx})}$$

where SD: standard deviation; r_{xx}: reliability.

To estimate the reliability, the ICC was used (26;27).

The dominant hand performed exercises during 18 minutes on the second day, the non-dominant hand did these on the third day. On the beginning of every test day and after the MVCs, subjective fatigue was assessed by means of a Visual Analogue Scale (VAS) for fatigue. While performing the tests, the participants were not encouraged by the examiner. The schematic overview of the applied protocol can be found in Figure 1.

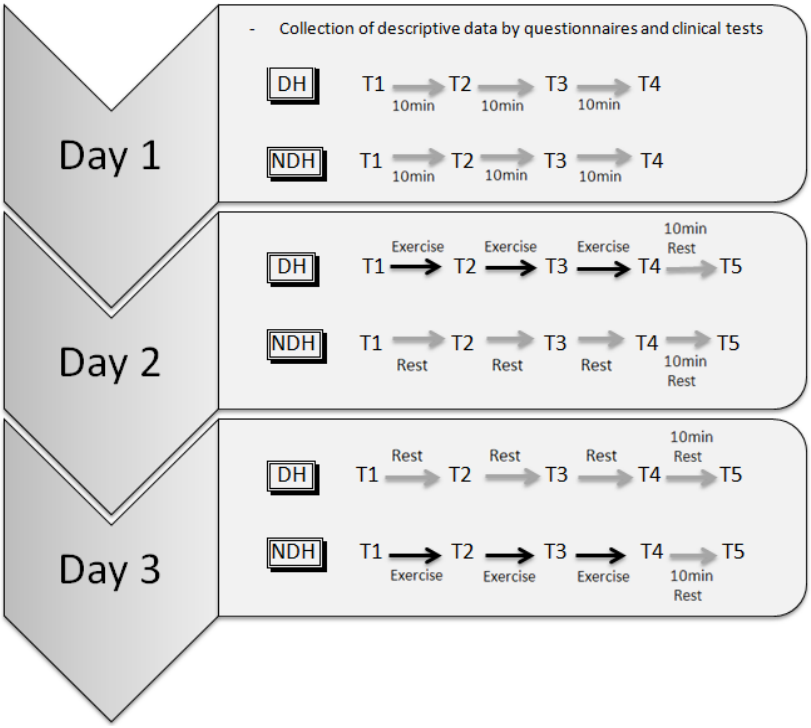

Figure 1. Overview of the experimental conditions.

DH: dominant hand; NDH: non-dominant hand; T: test moment

Experimental design

Test day one. Participants were introduced in the test procedure. Both hands performed force measurements on the e-link dynamometer (Figure 2), starting (T1) and finishing (T4) with an extended series of force measurements (Table 1). The extended series of force measurements (T1 and T4) included several different force measurements. First, two MVC at the e-link dynamometer, during five seconds with a rest interval of three seconds between the contractions, assessed in both the right and left arm. These contractions were followed by a sustained maximal hand grip contraction of 30 seconds, assessed in both arms. Afterwards, 30 brief maximal hand grip contractions were performed in a rhythm of one contraction per two seconds, in the right and left arm (9). The highest contraction force of the two MVC attempts in each hand were used as the two baseline MVC's for the right and left hand.

On test moment two (T2) and test moment three (T3), only MVC's were conducted by both hands. Between every test moment the subjects had a rest period of 10 minutes, when questionnaires were completed and the clinical tests were performed. Questionnaires and clinical tests were randomly conducted, except for the Box and Block Test (BBT), which was or the first conducted test or the last conducted test of the day. On test day one, independently of the hand dominance, the right hand started performing each grip measurement, followed by the left hand contractions.

Figure 2. The e-link dynamometer (Biometrics, Ltd.).

Test day two. On the second test day, the same measurements of neuromuscular fatigue were conducted. In contrast to the first test day, on T4 the sustained maximal hand grip contraction and the dynamic maximal handgrip contraction were only measured in the hand which performed the exercises and there were five test moments. Subsequent on T1, the dominant hand of the participant did a series of exercises at the e-link dynamometer where the hand has to adjust the grip force, with one minute breaks between the three exercises, (1) eclipse: two minutes holding a little ball in a moving bigger ball, (2) two minutes grasping bananas by monkeys, (3) two minutes catching falling balls on a bucket (Figure 3(a) to (c)). The order of exercises was similar for all subjects. The weight the participant had to press at the e-link dynamometer while exercising, was individually adjusted according to the maximal contraction performance of T1 on test day one. During the exercises the subject had to press at 15% to 25% of their baseline MVC.

After the exercise period, the MVC force was measured in both the right and left hand (T2), by performing a five seconds lasting MVC for two times. Further, this series of exercises and the same measurement of MVC force was executed in a total of three times, so the dominant hand performed exercises during 18 minutes. The non-dominant hand rested between the exercises.

To determine the neuromuscular fatigue recovery capacity, 10 minutes of rest were added after the fourth test moment (T4), after which the fifth test moment of force measurements (T5), which consisted of two maximal hand grip contractions for both the right and left hand, was accomplished. The five seconds holding MVC force in the hand was measured two times at both the right and left side of the subject (T5), to assess the level of recovery. The exercised (dominant) hand started performing each grip measurement.

Test day three. On the third test day, the same protocol as test day two was followed, with the non-dominant hand exercising and the dominant hand not. On test day three, the exercised, non-dominant hand started to perform each grip measurement.

Figure 3(a). Eclipse.

Figure 3(b). Monkeys.

Figure 3(c). Balls and bucket.

Figure 3. Exercises that were performed during two minutes for each game, at 15% to 25% of the maximal strength.

Table 1. Overview of the measurements on each test moment of each test day.

	Test moment	*1*	*2*	*3*	*4*	*5*
Day 1	DH+NDH	VAS 2x MVC 5 s VAS Sust.30 s Rep.30x/60 s	2x MVC 5 s VAS	2x MVC 5 s VAS	2x MVC 5 s VAS Sust.30 s Rep.30x/60 s	/
Day 2	DH+NDH	VAS 2x MVC 5 s Sust.30 s Rep.30x/60 s	2x MVC 5 s VAS	2x MVC 5 s VAS	2x MVC 5 s VAS *Only DH:* sust.30 s *Only DH:* rep.30x/60 s	VAS 2x MVC 5 s
Day 3	DH+NDH	VAS 2x MVC 5 s Sust.30 s Rep.30x/60 s	2x MVC 5 s VAS	2x MVC 5 s VAS	2x MVC 5 s VAS *Only NDH:* sust.30 s *Only NDH:* rep.30x/60 s	VAS 2x MVC 5 s

DH: dominant hand; NDH: non-dominant hand; PwMS: patients with multiple sclerosis; VAS: Visual Analogue Scale; MVC: maximal voluntary contraction; Sust.: sustained contraction; Rep.: repetitive contractions; s: second

Outcome measures

Descriptive outcome measures. The collected personal characteristics were: age, gender, height, weight, profession, hobbies, co-morbidity and the use of medication. The Expanded Disability Status Scale (EDSS) score, determined by a neurologist, was registered for the patients with MS.

The Edinburgh Oldfield Handedness Inventory (EOHI) determined the dominant hand of the subjects (22). The strength of the arm muscles (pinch grip, elbow flexion, shoulder abduction) was assessed with the Motricity Index (MI, normal score=100) (28). The Modified Ashworth Scale (MAS) was used to evaluate muscle tone in the wrist flexors and wrist extensors (no increase in muscle tone score=0, rigid body part score=4) (29). The Fahn's tremor rating scale was used to screen for the presence of intention tremor, which could have an influence on the results of the study (30). To assess the unilateral gross function and manual dexterity, the Box and Block Test (BBT) was applied (31).

The Neurological Fatigue Index for Multiple Sclerosis (NFI-MS) measured the severity of fatigue in patients with MS (strongly disagree score=0, strongly agree score=3) (6). The Modified Fatigue Impact Scale (MFIS, never score=0, almost always score=4) provided the impact of fatigue on daily life of the subjects (32). The Barthel Index (BI) evaluated the activities of daily life (normal score=20) (33). The daily activities of the previous days were recorded.
The Beck Depression Inventory-Fast Screen (BDI-FS) assessed the presence and degree of depression (34). The switching attention and processing speed of the subjects was evaluated by the Symbol Digit Modalities Test (SDMT, mean score ranges between 35,8 and 58,2) (35).

Experimental outcome measures. The experimental outcome measures were the maximal grip strength, the static and dynamic fatigue indices and the subjective experience of fatigue.

Hand grip strength. The isometric force (kg) was recorded by a hand held e-link dynamometer (Biometrics, Ltd) (23;36). The hand span of the dynamometer was set standard on handle position two (23). The starting position was based on the recommends of the American Society of Hand Therapists. The subjects were sitting upright, shoulder in adduction and neutrally rotation, an elbow flexion at 90°, forearm in neutral position and the wrist between 0° en 30° of dorsiflexion (23;37).

Maximal sustained hand grip contraction. Healthy controls and the patients with MS had to produce maximal sustained handgrip contractions of 30 seconds on the e-link dynamometer. This was used to investigate the static neuromuscular fatigue. The slope is an indication of the rate of fatigue. To calculate a static fatigue index (SFI), the area under the force-versus-time curve was compared with the theoretical curve that would be seen if there is no neuromuscular fatigue (throughout the sustained contraction, the maximal initial force is maintained) (9). The SFI ranges from 0-1. The higher the index, the more fatigue there is.

Maximal dynamic hand grip contraction. Based on the methodology as used by Schwid et al., subjects performed series of 30 brief maximal contractions in a rhythm of one contraction per two seconds (9). To calculate a dynamic fatigue index (DFI), the maximal of the three last MVC's achieved during the repetitive contractions was divided by the maximal of the three first MVC's of the repetitive contractions. This value was subtracted from one to obtain the DFI. The DFI ranges from 0-1. The higher the index, the more fatigue there is.

Subjective experience. The subjective experience of the participants muscular fatigue in their right and left arm was noted on a VAS (not fatigue at all score=0, extremely fatigue score=10). At the start of each test day and after the MVC measurements of the test moments (T1-T4), a score on a VAS was indicated. On test day two and three, a score on the VAS was indicated immediately after the rest period of 10 minutes and before measuring the MVCs. The motivation of a subject may have an important influence on the performances. 'How motivated are you?' was asked twice on each test

day (at start, after T3) and scored on a VAS (not motivated at all score=0, extremely motivated score=10) (38).

Statistical analysis

Data were analysed using IBM SPSS statistics 22. The outcomes of the patients were compared with those of the age- and sex matched healthy subjects. To analyse these data, the parametrical t-test was used when the assumptions of normality and homogeneity of variance were met. If the assumptions were not met, a Mann-Whitney U test was applied. An evaluation of the changes of the outcome results over time, measured at one test day, were made. The evolution in the maximal hand grip strength, as well as in the sustained and dynamic contractions over time for each day, were analysed with a paired t-test and a one-way repeated measures analysis of variance or if a non-parametric test was required, with a Wilcoxon signed-ranks test and a Friedman two-way analysis of variance. An assessment of each group is made if recovery occurs, based on a paired t-test to analyse the change in grip force after a rest period. To compare the rate of recovery between the two groups, a Mann-Whitney U test was applied. To analyse the subjective feeling of neuromuscular fatigue of the participants over time for each test day, a Friedman two-way analysis of variance was used. The test-retest reliability of the maximal hand grip strength was assessed, based on the data of the MVCs of day 1, using the ICC. The between day variability was investigated, based on the first measured MVC, SFI and DFI on each test day, using the ICC. The SEM was calculated to determine the amount of variation in the measurement errors of the grip strength assessment and the fatigue indices. The level of statistical significance was set at $p<0,05$.

Results

Participants

Twenty patients with MS and 20 healthy controls participated in this study. The clinical characteristics of the MS patients and healthy controls are summarized in Table 2.

There were no statistically significant differences between the two groups on gender, age and body mass index. Seventeen healthy controls had a right hand dominance, one preferred the left hand in performing daily life activities and two controls of the 20 were ambidextrous. All patients with MS had a preference to use their right hand in activities of daily living. Significant differences were found in some clinical baseline characteristics between groups (Table 2). The patients with MS scored significant higher compared to healthy controls on the MFIS, NFI-MS, and BDI-FS. On the SDMT, BI, MI both dominant and non-dominant hand and on the BBT both dominant and non-dominant hand, healthy controls scored significantly higher in comparison with the patients affected by MS. None of the participants had marked spasticity, intention tremor, postural tremor or dysmetria.

According to Mathiowetz et al., the average performance of healthy males on the BBT, aged 57, is 75,2 cubes for the right hand and 73,8 for the left hand. The average performance of healthy females on the BBT, aged between 55 and 59 years, is 74,7 cubes for the right hand and 73,6 for the left hand. Both healthy controls and patients with MS scored on average below their standard values (39). Based on the significant difference between both groups on the score on the BBT, the degree of arm dysfunction is higher in the patients with MS as compared with the healthy controls.

To interpret the score on the MFIS, the cut-off value of 38 was used (40). Based on this value, 13 patients with MS suffered from fatigue while none of our healthy controls (mean score 11,40). Interpreting the Barthel Index, the patients with MS were on average moderately independent, they need help in performing some daily life activities (mean score between 10-14) (41).

According to Beck et al., the score zero (13 healthy controls) and one (four healthy controls) on the BDI-FS indicated minimal depression in these participants (score 0-3). Three healthy controls refused to fill in this questionnaire. Thirteen patients with MS were considered to have a minimal depression (score 0-3). Four patients with MS scored between four and six on the BDI-FS, which indicated mild depression. Two patients were considered to have a moderate depression (score 7-9). The score on the BDI-FS was missing of one patient with MS (42).

Based on the normative data for the SDMT, a screening instrument for cognitive impairment, processing speed, healthy participants (mean score 42,45) scored, looking at the average group age of about 57 years, higher than the reference value (score 35,80), while patients with MS scored below this value (32,40) (35).

Table 2. Clinical characteristics of the healthy subjects and patients affected by MS.

	Controls (n=20)	*Patients with MS (n=20)*	*P-value*
Gender M/FM	7/13	7/13	na
Age (years)	57,10 ± 13,75	57,30 ± 13,66	0,963
Body mass index	24,94 ± 3,82	25,28 ± 2,95	0,775
Diagnosed with MS (years)	na	17,76 ± 15,14	na
EDSS (0-10)	na	4.41 ± 1.74	na
Handedness L/R/Ambi	1 / 17 / 2	0 / 20 / 0	na
MI DH (0-100)	99,10 ± 2,77	94,05 ± 9,47	0,025
MI NDH (0-100)	98,30 ± 3,50	89,55 ± 11,80	0,008
Spasticity DH P/A	0 / 20	0 / 20	na
Spasticity NDH P/A	0 / 20	2 / 18	na
Manual dexterity DH (0-150)	64,35 ± 9,69	47,70 ± 10,88	0,000
Manual dexterity NDH (0-150)	64,35 ± 9,19	46,40 ± 13,73	0,000
NFI-MS (0-69)	13,70 ± 9,41	41,50 ± 13,59	0,000
MFIS (0-84)	11,40 ± 9,47	42,70 ± 16,14	0,000
BI (0-20)	19,87 ± 0,35	14,56 ± 5,59	0,001
Emotional status (0-21)	0,24 ± 0,44	2,68 ± 2,75	0,001
Cognitive status (0-110)	42,45 ± 15,17	32,40 ± 12,11	0,026

Mean ± standard deviation are shown.

M: male; FM: female; y: years; EDSS: Expanded Disability Status Scale; L: left; R: right; Ambi: ambidextrous; MI: Motricity Index; NFI-MS: Neurological Fatigue Index-MS; MFIS: Modified Fatigue Impact Scale; BI: Barthel Index; DH: dominant hand; NDH: non-dominant hand; P: present; A: absent; na: not applicable.

Occurrence of neuromuscular fatigue during exercise protocols

Objective assessment of neuromuscular fatigue

Fatigue and recovery during exercise. The mean values of grip force for each test moment on test day one, test day two and test day three, are shown in Table 3. The significance values to assess the evolution in the maximal handgrip strength over time for each test day, split up for both groups and for both hands, were analysed. On test day one (Figure 4(a) and (b)), the MVC didn't change significantly over time ($p>0,05$). On test day two, the MVC of the exercising dominant hand decreased significantly over time in both the healthy controls ($p<0,001$) and patients with MS ($p<0,001$). The changes in grip force for the dominant and non-dominant hand are shown in respectively Figure 4(c) and (d). The MVC of the non-dominant hand decreased significantly over time on test day three, when the non-dominant hand performed the exercise protocol, in both the healthy controls ($p<0,001$) and patients with MS ($p<0,001$). The changes in grip force on test day three are shown in Figure 4(e) and (f).

Notable, in the patients with MS, the MVC (T1-T4) changed significantly over time only in the hand which performed the exercises (dominant hand on test day two ($p<0,001$), non-dominant hand on test

day three (p<0,001)). In healthy controls on both test day two and three, in both the exercised hand as in the non-exercised hand, the maximal handgrip strength changed significantly over time (p<0,05).

Table 3. Overview of the mean value of grip force (kg) for each test moment on test day one, test day two and test day three.

			T1	*T2*	*T3*	*T4*	*T5*	*p-value (T1-T4)*
Day1	DH	Controls	35,43±10,48	34,82±10,87	33,99±10,39	34,17±9,93	/	P=0,054
		PwMS	26,18±9,53	25,15±10,66	25,57±8,71	26,40±9,43	/	P=0,162
	NDH	Controls	32,71±9,89	33,30±10,13	32,63±10,33	32,06±10,32	/	P=0,722
		PwMS	23,82±9,45	23,10±9,80	22,64±9,31	22,31±9,18	/	P=0,158
Day2	DH	Controls	33,90±8,64	27,97±6,90	27,15±8,02	27,55±8,13	30,00±8,11	P<0,001
		PwMS	26,01±9,33	23,42± 9,34	21,42± 9,71	21,57±9,88	23,71±10,23	P<0,001
	NDH	Controls	32,23±9,80	29,74±9,55	29,75±9,79	30,38±10,08	28,77±9,89	P=0,001
		PwMS	22,84±9,24	22,42±9,03	22,33±8,49	21,15±8,88	22,55±10,20	P=0,460
Day3	DH	Controls	33,07±10,28	30,94±10,32	31,68±10,31	31,34±9,32	31,43±10,52	P=0,022
		PwMS	25,54±9,91	25,91±10,29	24,76±11,16	24,56±9,63	25,01±10,99	P=0,852
	NDH	Controls	30,79±10,30	28,01±10,21	26,87±9,50	26,20±10,25	27,78±9,78	P<0,001
		PwMS	22,49±9,34	20,16±8,79	18,58±8,54	18,13±8,09	21,24±10,13	P<0,001

Mean ± standard deviation are shown.
DH: dominant hand; NDH: non-dominant hand; PwMS: patients with multiple sclerosis; T: test moment.
The data of the exercised hand is highlighted in grey; the vertical line shows the rest period of 10 minutes between T4 and T5.

To analyse what the difference is in grip force before and after performing exercises or without doing exercises in the meantime, the difference score between MVC T1 and MVC T4 was calculated, for both test day two and three. The mean outcome of the subtraction was in both groups significant higher in the exercised hand as compared with the non-exercised hand (test day two controls p=0,004; test day two PwMS p=0,012; test day three controls p=0,013; test day three PwMS p=0,002). The mean difference in force as result of the subtraction of the MVCs before and after performing exercises or after a period of rest, was 6,35 kg in the dominant (exercised) hand of healthy controls and 1,85 kg in the non-dominant (relaxed) hand of healthy controls on test day two. In patients with MS the mean difference in force of the measurement at start and at the end of the test day, was 4,40 kg in the dominant (exercised) hand and 1,48 kg in the non-dominant hand. On test day three, the mean difference in force as result of the subtraction of the MVCs before and after performing exercises or after a period of rest, was 4,58 kg in the non-dominant (exercised) hand of healthy controls and 1,73 kg in the dominant (relaxed) hand of healthy controls. In patients with MS the mean difference in force was 4,36 kg in the non-dominant (exercised) hand and 0,98 kg in the dominant hand. The group difference between healthy controls and patients with MS was determined with a Mann-Whitney U test (test day two) and an unpaired t-test (test day three). On both test day two and

three , in the dominant hand (test day two p=0,148; test day three p=0,390) as well as in the non-dominant hand (test day two p=0,332; test day three p=0,854), grip force over time did not decline more in patients with MS as compared to healthy controls.

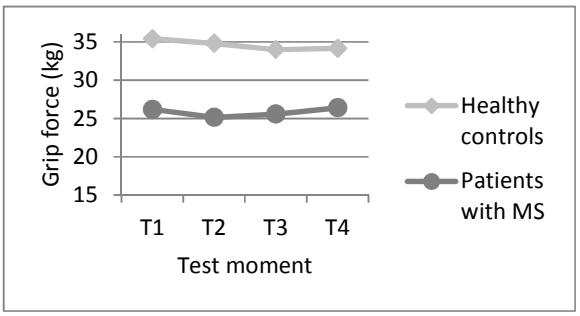

Figure 4(a).

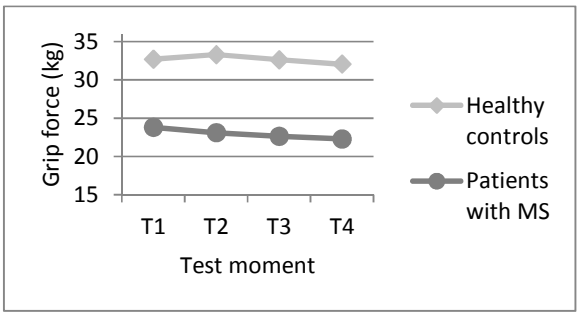

Figure 4(b).

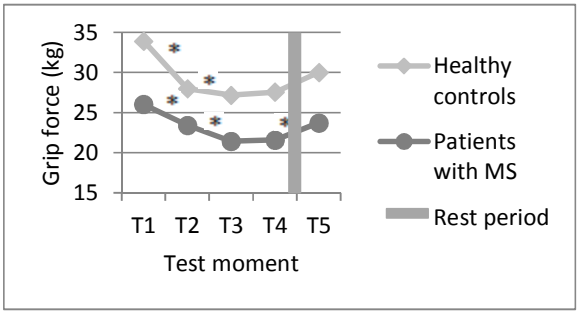

Figure 4(c).

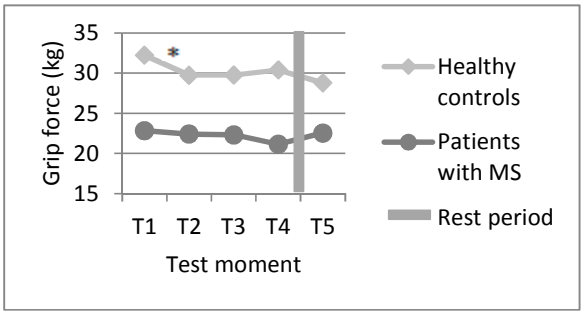

Figure 4(d).

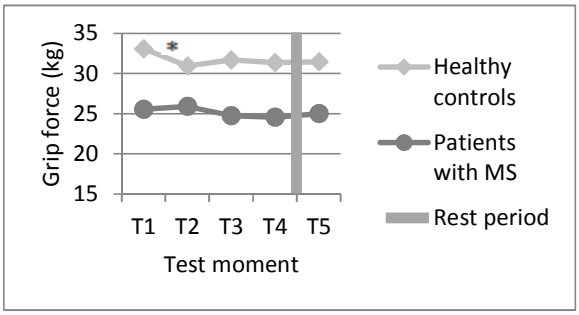

Figure 4(e).

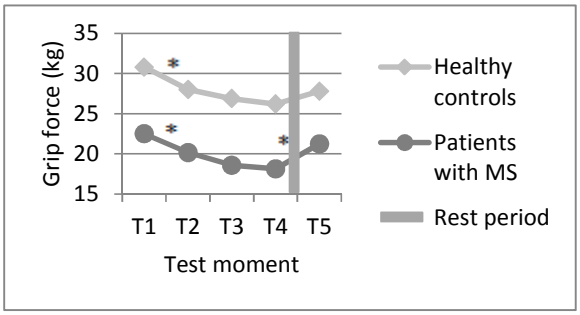

Figure 4(f).

Figure 4. The mean values of the MVCs of the healthy controls and patients with MS. Grip force evolution of the dominant hand (Figure 4(a)) and the non-dominant hand (Figure 4(b)) on test day one, of the dominant (exercised) hand (Figure 4(c)) and non-dominant hand (Figure 4(d)) on test day two, and grip force evolution of the dominant hand (Figure 4(e)) and non-dominant (exercised) hand (Figure 4(f)) on test day three. * $p<0,05$ for the difference between the two test moments.

To determine the neuromuscular fatigue recovery capacity, the MVC on T4 was compared with the MVC on T5 of both test day two and three, in both groups for each hand. On test day two, the MVC measured after performing the exercises didn't change significantly after a 10 minutes rest period

(p>0,05), for both hands of the healthy controls and for the non-dominant hand of the patients with MS. However, the dominant hand (exercised hand) of the patients with MS performed a significant higher MVC on T5 as compared with the MVC on T4 (p=0,001), which indicates recovery after 10 minutes of rest. On test day three, for both the dominant and non-dominant hand of the healthy controls and for the dominant hand of the patients with MS, the MVC on T5 did not change significantly regarding the MVC on T4. In contrast, the exercised non-dominant hand of the patients with MS showed a significant higher MVC on T5 (p=0,001) in comparison with the MVC measured just after performing the exercises (T4). Notable, the exercised hand in patients with MS showed recovery in force after 10 minutes of rest. The grip force in healthy controls did not increase significantly after a rest period of 10 minutes.

To analyse the extent of recovery in the hand which performed the exercises, in healthy controls in comparison with patients affected by MS, the quotient of MVC T5 on MVC T4 of the healthy controls was compared with the quotients of the patients with MS, both for test day two and test day three. On test day two, there is no significant difference in the recovery rate of the dominant hand between healthy controls and patients with MS (p=0,465), as well as no significant difference was found in the recovery rate of the non-dominant hand between both groups on test day three (p=0,273).

Static fatigue index. The differences in SFI between healthy controls and patients with MS, of each test moment (T1, T4) on each test day (D1, D2, D3) were interpreted. On every SFI measurement, the patients with MS scored significantly higher than the healthy controls (p<0,05) indicating that there was more neuromuscular fatigue in patients.

The significance value of the comparison in SFI between the first SFI measurement (T1) and the last SFI measurement (T4) on each test day is evaluated, to check for influence of exercises on the SFI. The SFI didn't change significantly during each test day, for both the healthy controls and the patients with MS (p>0,05). Table 4 shows the means of the SFI measurements on T1 of each test day. The SFIs of T1 were used to assess the reliability of the measurement.

Dynamic fatigue index. The significance values of the comparison in DFI between healthy controls and patients with MS, of each test moment (T1, T4) on each test day (D1, D2, D3) were interpreted. On every DFI measurement, except two test moments, there is no significant difference in the DFI between healthy controls and patients with MS (p>0,05). On the first DFI measurement of test day one and test day three, in respectively the non-dominant hand (p=0,038) and the dominant hand (p=0,028), the patients with MS showed a significantly higher DFI as compared with healthy controls.

The significance values of the comparison in DFI between the first DFI measurement (T1) and the last DFI measurement (T4) on each test day were interpreted. On test day one, there is a significant difference between the DFI at T1 and T4. In healthy controls, for both the dominant (p=0,044) and the non-dominant hand (p=0,030), the DFI increased significantly at T4 as compared with T1, indicating that there was more neuromuscular fatigue at T4. In patients affected by MS, the DFI of the dominant hand on test day 1 was significantly higher (p=0,010) at T4, as compared with the DFI on T1. On test day two and three, the DFI didn't change significantly during each test day, for both the healthy

controls and the patients with MS (p>0,05). In table 4, the mean of the DFI measurements on T1 of each test day are shown. The reliability of the measurement was assessed based on the DFI of T1 of each test day.

Table 4. The mean of the SFI and DFI measured at test moment one, on each test day. The defined ICC.

		Day 1	*Day 2*	*Day 3*	*ICC*
	SFI				
DH	Controls	0,30±0,10	0,28±0,10	0,26±0,17	0,578
	PwMS	0,42±0,10	0,42±0,07	0,43±0,10	0,715
NDH	Controls	0,31±0,11	0,30±0,10	0,28±0,14	0,641
	PwMS	0,37±0,09	0,43±0,11	0,42±0,12	0,750
	DFI				
DH	Controls	0,23±0,10	0,24±0,11	0,19±0,12	0,369
	PwMS	0,26±0,11	0,24±0,14	0,27±0,12	0,506
NDH	Controls	0,24±0,09	0,29±0,10	0,23±0,12	0,580
	PwMS	0,32±0,11	0,30±0,13	0,31±0,15	0,674

Mean ± standard deviation are shown.

SFI: static fatigue index; DFI: dynamic fatigue index; ICC: intraclass correlation coefficient; DH: dominant hand; NDH: non-dominant hand; PwMS: patients with multiple sclerosis.

Subjective experience of neuromuscular fatigue

Subjective reports on muscle fatigue. To represent the subjective feeling of neuromuscular fatigue, a score on a VAS was questioned. Table 5 shows the median value of the subjective feeling of muscle fatigue on each test moment of each test day, for both the healthy controls and patients affected by MS. The significance values to assess the evolution in the subjective feeling of neuromuscular fatigue over time for each test day, split up for both groups and for both hands, were obtained by applying a Friedman two-way analysis of variance.

On test day one, the subjective feeling of muscle fatigue increased significantly in both the dominant (p<0,001) and non-dominant hand (p<0,001) of healthy controls. On the first test day, when no exercises were performed, there was no significant change over time in any hand in the subjective feeling of muscular fatigue in patients with MS.

On test day two, healthy controls had a significant increase (p<0,001) over time in the sensation of muscle fatigue, in both the dominant (exercised hand) as the non-dominant hand. Patients with MS scored on test day two only in the dominant (exercised) hand a significant increase (p<0,001) in the feeling that their muscles became more fatigued.

On the last test day, only the non-dominant, exercising hand of the healthy controls showed a significant increase (p<0,001) in the feeling of muscle fatigue, while in patients with MS, both the dominant (p=0,012) and non-dominant (exercised) hand (p<0,001) showed a significant increase in

their feeling of muscle fatigue over time. The dominant hand of healthy controls showed no significant changes (p=0,247) in the sensation of muscle fatigue over time.

Table 5. Overview of the median value and the quartiles of the subjective feeling of neuromuscular fatigue (VAS) at start of the day and after each test moment, on test day one, two and three.

			T1	*T2*	*T3*	*T4*	*T5*	*P-value*
Day1	DH	Controls	0,50 [0,00;2,00]	2,00 [0,00;3,00]	2,00 [1,00;3,00]	2,00 [1,00;4,00]	5,00 [1,75;7,00]	0,000
		PwMS	2,50 [0,75;6,00]	4,00 [0,00;5,50]	3,00 [0,00;5,00]	5,50 [0,00;7,00]	6,00 [3,75;7,25]	0,157
	NDH	Controls	1,00 [0,00;2,00]	2,00 [0,00;4,00]	2,00 [1,00;3,00]	3,00 [1,00;5,00]	4,50 [1,75;7,00]	0,000
		PwMS	3,50 [1,75;7,00]	5,00 [2,25;7,50]	3,00 [0,00;5,50]	5,00 [2,00;6,25]	6,00 [3,00;7,25]	0,149
Day2	DH	Controls	0,00 [0,00;1,00]	2,00 [0,25;3,00]	2,50 [1,25;3,75]	3,00 [2,00;5,75]	2,50 [0,25;3,75]	0,000
		PwMS	1,50 [0,00;2,75]	3,00 [1,50;6,00]	4,00 [2,50;7,00]	4,00 [3,00;8,00]	4,00 [2,00;7,75]	0,000
	NDH	Controls	0,00 [0,00;1,00]	2,00 [0,00;2,00]	2,00 [1,00;3,00]	2,00 [1,00;5,00]	2,00 [0,00;4,00]	0,000
		PwMS	0,00 [0,00;3,50]	2,50 [0,75;6,00]	2,00 [0,00;5,25]	1,50 [0,00;6,50]	2,50 [0,00;5,75]	0,095
Day3	DH	Controls	1,00 [0,00;3,00]	1,00 [1,00;4,00]	3,00 [1,00;4,25]	3,00 [1,00;5,00]	2,00 [1,00;4,00]	0,247
		PwMS	1,00 [0,00;2,00]	2,00 [0,50;4,00]	2,00 [0,50;5,50]	2,00 [0,50;8,00]	2,00 [0,50;6,50]	0,012
	NDH	Controls	1,00 [0,00;2,75]	2,00 [1,00;3,75]	3,00 [2,00;5,00]	4,00 [1,00;5,00]	2,50 [1,00;4,75]	0,000
		PwMS	2,00 [0,25;3,75]	4,00 [2,25;6,75]	5,50 [3,00;7,00]	7,00 [3,50;8,00]	5,00 [2,00;7,00]	0,000

Median [quartile 25‰;75‰] are shown.

DH: dominant hand; NDH: non-dominant hand; PwMS: patients with multiple sclerosis; T: test moment.

The data of the exercised hand is highlighted in grey; the vertical line shows the rest period of 10 minutes between T4 and T5.

Reliability of muscle strength and fatigue indices

Within and between day reliability. To look at the test-retest reliability of the maximal hand grip strength, the four MVC measurements of test day one were analysed, based on the ICC (two-way mixed model) with a confidence interval of 95%. The ICC for the total set of measurements of both the healthy controls and patients with MS was 0,991. In analysing the consistency in measurements,

separated for the dominant hand and non-dominant hand and for the healthy subjects and patients with MS, the ICCs were very high (Table 6).

To assess the between day variability in this study, the first MVC measurements of each test day were analysed, based on the ICC (two-way mixed model) with a confidence interval of 95%. The ICCs, analysed for both hands and both groups apart, are also shown in Table 6. These coefficients indicated a good reliability. Also the first measured SFI on each test day, separated for the dominant hand and non-dominant hand and for the healthy subjects and patients with MS, were analysed on the same way as the ICC of the MVCs, to evaluate the between day variability. This resulted in an ICC ranging between 0,50 and 0,75 (Table 4), which gave an indication for moderate reliability. Additionally, the variability between the first DFI measurements of each test day was analysed using the ICC. The ICCs, separated for the dominant hand and non-dominant and for the healthy subjects and patients with MS, are shown in Table 4. These coefficients gave an indication of poor to moderate reliability.

Table 6. The within and between day reliability based on the maximal hand grip strength, the defined ICC.

MVC	Test day 1 – all test moments	*ICC*
DH	Controls	0,993
	PwMS	0,985
NDH	Controls	0,991
	PwMS	0,989
MVC	Test moment 1 – each test day	*ICC*
DH	Controls	0,876
	PwMS	0,961
NDH	Controls	0,951
	PwMS	0,954

ICC: intraclass correlation coefficient; DH: dominant hand; NDH: non-dominant hand; PwMS: patients with multiple sclerosis.

Standard error of measurements. To determine the amount of variation in the measurement errors of the experimental outcome measures, the SEM was calculated, based on the formula earlier described. The ICC of the MVCs, regardless of the hand dominance, was 0,913 for the healthy controls and 0,958 for the patients with MS. The standard deviation of the MVCs at T1 of test day one, two and three was 9,812 kg for the healthy controls and 9,382 kg for the patients with MS. The calculated SEM for the MVC was 2,89 kg in the healthy controls and 1,92 kg in the patients with MS. The lower the level of SEM, the higher the level of score accuracy (43).

The ICC of the SFI measurements at T1 of each test day, irrespective of the hand dominance, was 0,603 for the healthy controls and 0,731 for the patients with MS. The standard deviation of the SFIs at T1 of all three test days was 0,121 for the healthy controls and 0,098 for the patients affected by MS.

The SEM for the SFIs was, based on the previous formula, 0,076 in the healthy controls and 0,051 in the patients with MS.

The SEM for the DFIs measured at T1 of test day one, two and three was 0,080 in the healthy controls and 0,079 in the patients with MS, where the ICC was, regardless of the hand dominance, 0,467 for the healthy controls and 0,608 for the MS patients, and where the standard deviation was 0,109 for the healthy controls and 0,126 for the patients with MS.

Discussion

The applied protocol of performing exercises and hand grip contractions could provoke and detect objectively neuromuscular fatigue in healthy controls and patients affected by MS. Recovery in neuromuscular fatigue, after a rest period of 10 minutes, only occurred in the exercising hand of the patients with MS. The grip strength and fatigue indices could be considered as reliable.

Occurrence of neuromuscular fatigue during exercise protocols

The influence of MS on the feeling of fatigue has been previously investigated (44). Fatigue is a commonly reported and debilitating symptom with a subjective nature. No gold standard exists to measure fatigue (45). Objective changes in performance caused by fatigue can be measured by quantifying the decline in an aspect of the performance during a prolonged activity or by comparing the performance before and immediately after a prolonged fatigue-inducing task (46). In the present study, the presence of neuromuscular fatigue after performing an exercise protocol was investigated. Differences between the healthy control group and MS patients were explored.

According to previous studies, signs of neuromuscular fatigue in MS patients could be demonstrated by a decline in force in isometric and isotonic contraction (47;48). The applied protocols consisted of only a few contractions. To our knowledge, no study has been reported the investigation of the difference in force decline between patients with MS and healthy controls, when performing a fatigue protocol over a longer period of time. If the assumption is made that when the maximal handgrip strength significantly declines over time, neuromuscular fatigue occurs, than neuromuscular fatigue appeared in the hand which performed the exercises. The difference in terms of percentage of the first maximal grip strength and the maximal handgrip strength after performing exercises was, on test day two, 19% in the dominant hand of the healthy controls and 17% in the dominant hand of the patients with MS. On test day three, this difference was 15% in the non-dominant hand of healthy controls and 19% in the non-dominant hand of patients with MS. Considering this finding, the applied protocol of approximately 20 minutes doing exercises could elicit neuromuscular fatigue, in both the dominant and non-dominant hand. Notable is the result that in both the exercised and the relaxed hand of the healthy controls, a significant decline in grip strength over time occurred. The decline in maximal grip strength in the exercising hand was larger than the decline in grip strength of the relaxed hand. This is in line with Doix et al., who reported a cross-over effect of muscle fatigue on the contralateral limb. In the study of Doix et al., unilateral fatiguing contractions induced immediately a maximal torque reduction in the exercising limb and postponed a loss of torque production in the non-exercising contralateral limb (49). Based on the assumption, in healthy controls after performing an exercise protocol in one hand, neuromuscular fatigue occurred in both hands, independently if the hand exercised or not. This may relate to the findings of Morrison et al., who reported that following exercise-induced fatigue of the wrist extensors in a single arm of healthy subjects, an increase in the muscle activity of the forearm (EMG) in both arms was seen (50).

The difference scores before and after the entire exercise protocol gave an idea about the degree of neuromuscular fatigue. These differences were higher than the SEM on each day for the

exercised hand, but not for the non-exercised hand. Remarkable, the difference score between MVC T1 and MVC T4 in the non-dominant (relaxed) hand of test day two varied just 0,37 kg between the healthy controls (MVC T1 – MVC T4= 1,85 kg) and patients with MS (MVC T1 – MVC T4= 1,48). However, the maximal handgrip strength of the non-dominant hand of the healthy controls on test day two changed significantly over time, whereas this change of the maximal hand grip strength over time was not significant in the patients with MS.

The variation in grip force, per test day, before and after performing all exercises or after a period of rest, was not significantly different between healthy controls and patients with MS. Regarding the MVCs (T1,T4), there is surprisingly no significant difference in the degree of provoked neuromuscular fatigue between both groups after an exercise protocol at low intensity (15-25% of the MVC). According to Iyengar et al., healthy controls apply 11% of the maximal force during manipulative tasks in daily life, while patients with MS apply 20% of their maximal force during the performance of functional tasks (21). Maybe an exercise protocol over a longer period of time or at higher intensities could provoke more force decline in patients with MS, and not in healthy controls.

In analysing the neuromuscular fatigue recovery capacity, healthy controls didn't show a significant increase in grip force after a rest period of 10 minutes. Remarkable, the exercised hand in patients with MS did show recovery in force after 10 minutes of rest. The results are in contrast to the finding of de Haan et al., who reported a recovery, though incompletely, in the maximal rate of force of the quadriceps muscles, in both healthy controls and patients with MS after nine minutes of recovery. However, also in their study, with electrical stimulation, the patients affected by MS did not show a slower recovery of force after the fatigue protocol, but actually a faster recovery (47).

Several studies demonstrated the use of subjective questionnaires to rate the level of fatigue (15). Based on the subjective questionnaires (MFIS, NFI-MS, BI), the patients with MS indicated having more (influence of) fatigue in performing daily life activities, as compared with the healthy controls. Furthermore, the patients affected by MS showed a degree of arm dysfunction, if based on clinical tests collected on test day one (grip strength, MI, BBT).

Overall, in persons with MS, the subjective perception of fatigue in the arm was increasing when an exercise protocol was executed with that arm. In absence of exercising, scores remained stable. The healthy controls were not consistent in the indicated scores of their feeling of muscle fatigue. This may relate to the findings of Adamo et al., who reported that in healthy controls the subjective evaluations of sustained and intermittent grip exertions may not be a reliable indicator of muscle fatigue (51). A possible reason for the increasing feeling of fatigue in healthy controls on test day one, can be the unfamiliarity with the E-link dynamometer. The scores on the VAS on each test moment were analysed, to check if the patients with MS started with a higher score on the VAS (higher feeling of fatigue) as compared with the scores of the healthy controls. The results showed that persons with MS already reported more muscular fatigue in their arms than healthy controls, even before the execution of tests and exercises. On test day three, the MVCs of the healthy controls decreased significantly over time in both hands, while the feeling of neuromuscular fatigue increased significantly only in the non-dominant hand. The MVCs of the patients with MS decreased significantly over time only in the non-dominant hand. However, the patients reported an increased feeling of

fatigue in the muscles in both hands. According to Kluger et al., the actual performance and the perception of fatigue are distinct and potentially independent (46).

Reliability of muscle strength and fatigue indices

In order to check if exercise was able to elicit neuromuscular fatigue, repeated MVCs were asked, according to Dobkin (12). The MVC didn't change significantly over time, on test day one. This is to be expected because no exercise protocol was performed, only questionnaires and some clinical tests were administered. The stable scores on the MVCs proved that an adequate rest period was provided and the test itself did not provoke a fatigue effect. Additionally, it proved the absence of learning effects of the test. Hand grip strength has proven to be reliable in both healthy controls and patients with MS (10). Regarding the reliability of measurement, based on the MVC measurements of test day one, the test-retest reliability was good. The ICCs of the first measured SFI and DFI on each test day gave an indication for moderate test-retest reliability. This is in line with Schwid et al., who reported good test-retest reliability in MS patients for isometric strength, a moderate to good reliability in protocols that involved sustained contractions and a poor reliability in protocols involving repetitive contractions (9). The findings about the SFI suggest that patients with MS experienced more neuromuscular fatigue during a 30 seconds sustained maximal hand grip strength measurement in comparison with healthy controls. A future perspective is to define a cut-off value to decide if neuromuscular fatigue is present (9;11).

Limitations and future research

This study showed a good within day reliability of the hand grip force and a moderate to good between –day reliability of the hand grip force and fatigue indices. Despite this high reliability, some methodological considerations need to be addressed. The participant was not tested at a fixed moment of the day. Patients could have had a therapy session before the tests and healthy controls may have been tested after their occupation. This may have influenced the arm performance.

Sitting with the elbow in 90° flexion produces a higher grip strength than performing a hand grip contraction in fully elbow extension (52). It is important to standardise the measurements in the future. In this study, some patients with MS used the armrest of their wheelchair, other patients sat on a chair without armrests. The healthy controls sat on different chairs with or without armrests, depending on the location of testing. According to Hillman, the contraction force is significantly higher if the arm is unsupported, as compared to hand grip contractions performed with a supported elbow (53).

A larger sample size is needed to make sub analysis on the relation between the severity of arm dysfunction (muscle weakness) and the force decline (fatigue indices).

The intensity to provoke neuromuscular fatigue varies between several studies (11;54). It would be interesting to investigate the occurrence of neuromuscular fatigue when the participants have to perform this protocol at a higher intensity (> 25% of MVC) or for a longer duration. To investigate if other significant differences would appear between healthy controls and patients with MS.

Conclusion

To conclude, this exercise protocol could create neuromuscular fatigue in the hand muscles, based on a significant decrease of the maximal hand grip force over time, in both healthy controls and patients affected by MS. After 10 minutes of rest, only the patients with MS showed a significant recovery in force in the hand which performed the exercises.

The investigation of the psychometric properties of the hand grip force and fatigue indices showed a moderate to good reliability.

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