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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

The quantification of motor fatigability in the upper limb in persons with multiple sclerosis

Promotor :
Prof. dr. Peter FEYS

Copromotor :
Mevrouw Deborah SEVERIJNS

Caroline Lismont

Scriptie 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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The quantification of motor fatigability in the upper limb in persons with multiple sclerosis

Student: LISMONT Caroline

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Acknowledgement

I would like to take this opportunity to express my sincere thanks to several people who helped me realize this master thesis.
Firstly, I would like to thank Ms. Severijns, co-supervisor of my master thesis, for her invaluable guidance throughout this study. I am grateful to her for taking the various tests and her assistance during the writing process. Her constructive criticism, advice and insightful comments provided a significant contribution to the creation of this thesis.

Secondly, I would like to express my gratitude to all the subjects who participated in the study as they provided us with the necessary data to conduct this research.

Thirdly, a special tanks to E. Diricks, for taking the time to revise my master thesis.

And last but not least, I would like to express a warm thanks to my parents for their continuous support throughout the study.

Borgloon, 2016 C.L.

Research context

Fatigability after physical efforts occurs to everyone. This can manifest itself in a lack of muscle strength or muscle pain. It seems that motor fatigability occurs faster and persists longer with a disabling impact on daily life activities in individuals with multiple sclerosis (MS). We can objectively measure fatigability in different ways. Fatigability can be measured both in the upper and lower limb with repeated contractions, a sustained contraction and after or during a functional activity. A commonly used method is to calculate a fatigue index with a sustained contraction of 30 seconds, called the static fatigue index. This index determines the degree of fatigability of the muscle groups. The purpose of this study is to examine possible differences in motor fatigability of the upper limb in persons with multiple sclerosis. To do this, we use a static fatigue index.

This study is a mono-master thesis and is situated within a current research project, namely a doctoral study by Ms. Severijns, entitled "Motor fatigue during upper and lower extremity function in multiple sclerosis". The supervisor of this master thesis is prof. Dr. Feys, professor at the University of Hasselt and responsible for the Masters' Rehabilitation Sciences and Physiotherapy. Professor Dr. Feys is specialized in the treatment of patients with neurologic abnormalities in general and MS in particular.

This master thesis is part of the neurological domain within the Rehabilitation Research Centre (REVAL). The thesis is structured according to the central format.
The master thesis was conducted in REVAL in Diepenbeek in cooperation with the Rehabilitation and MS Centre in Overpelt. REVAL conducts research in virtually all fields of rehabilitation sciences, namely neurological, musculoskeletal, cardiorespiratory, pediatric and mental rehabilitation.

The study consisted of a constructive cooperation between the co-supervisor, Ms. Severijns and the thesis student. First they prepared together the study, they recruited the subjects and performed the testing. The data analysis was then carried out by both of them to reduce the risk of possible errors. Afterwards the student wrote the thesis independently and finally the co-supervisor checked the final version and improved if necessary.

Content

1. Abstract

Background: Motor fatigability is a frequently occurring symptom in persons with multiple sclerosis (MS). This motor fatigability can be measured both subjectively and objectively. Subjective measurements are often used, but largely interpreted emotionally. Objective measurements are very variable and not specifically defined. A commonly used method to measure motor fatigability is to calculate a fatigue index with a sustained contraction of 30 seconds.

Objectives: The main purpose of this study is to examine possible differences in motor fatigability of the upper limb in persons with MS. Another purpose is to investigate if there is a generalizability of motor fatigability in the different muscle groups of the upper limb. In addition this study also examines if there is an association between motor fatigability and the expanded disability status scale (EDSS), maximal strength and perceived difficulty to perform activities of daily life (ADL).

Methods: Persons with MS and healthy controls performed three maximal voluntary contractions and a sustained contraction of 30 seconds of the shoulder abductors, elbow flexors, handgrip and finger abductor in order to determine the maximal strength and static fatigue indexes.

Results: Twenty persons with MS and 20 healthy controls participated in the study. The mean EDSS score of the persons with MS was 3.4. There was a higher fatigability in the elbow flexors in persons with MS. Only fatigability of the finger abductor was significantly associated with the EDSS score. Elbow fatigability was almost significantly associated with the EDSS score, muscle strength and perceived difficulty to perform ADL. Additionally there was no generalizability of motor fatigability in the muscles of the upper limb.

Conclusion: Motor fatigability is not higher for persons with MS than healthy controls, except for the elbow flexors. Additionally motor fatigability could not be associated with EDSS score, maximal strength and perceived difficulty to perform ADL. As well there was no generalizability of fatigability in the muscles of the upper limb.

2. Introduction

"Multiple sclerosis (MS) is a chronic and progressive demyelinating disease of the central nervous system. The disease is characterized by a demyelination process that expresses itself in inflammation and damage of axons in the central nervous system"(Compston & Coles, 2002; Mollaoglu & Ustun, 2009). "This damage affects the conduction of nerve impulses in the central nervous system, which can cause a variety of symptoms. Depending on the affected area there may occur cerebellar-, motor-, sensory-, emotional- or sexual related symptoms". MS has a large impact on the life of the patient, mainly because of the unpredictability in progression and heterogeneous presentations of complaints (Compston & Coles, 2002; Mollaoglu & Ustun, 2009).

One of the frequently occurring symptoms of MS is fatigue (Kos, Kerckhofs, Nagels, D'Hooghe M, & Ilsbroukx, 2008). Fatigue can be defined as a lack of physical and/or mental energy that interfere with daily activities (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Although numerous studies have attempted to evaluate MS related fatigue, the exact cause of this symptom is not clear (Ghajarzadeh et al., 2013). Fatigue is a subjective characteristic without a uniform definition (Braley & Chervin, 2010).

A subconcept of this general fatigue is motor fatigability. Motor fatigability can be defined as a decline in the ability of the muscles to produce force or power after an exercise or sustained use, regardless of whether the task can be sustained (Dobkin, 2008). Patients with MS frequently suffer from motor fatigability (Krupp, Serafin, & Christodoulou, 2010). Most approaches to fatigability assessment can be classified as either subjective or objective (Krupp & Christodoulou, 2001). The subjective evaluation is based on questionnaires (self-report), while the objective evaluation is based on the loss of the maximal capacity of the muscles to generate force during exercise (Krupp & Christodoulou, 2001; Krupp et al., 2010). These self-report questionnaires, such as the Modified Fatigue Impact Scale (MFIS) or Fatigue Severity Scale (FSS), are by far the most common method to assess general fatigue. These questionnaires are readily available to the healthcare provider and their patients and can be implemented quickly (Krupp & Christodoulou, 2001; Krupp et al., 2010). Some of the questionnaires for general fatigue divide fatigue into mental and physical components and can in that way evaluate motor fatigability. Measurements based on self-reports are often interpreted in an emotional manner by the patient and the caregiver, allowing them to give

an inaccurate representation (Krupp & Christodoulou, 2001). Because of this limitation there are more accurate, objective methods needed to determine fatigability in persons with MS (Schwid, Covington, Segal, & Goodman, 2002). Fatigability can objectively be measured in different ways: fatigability can be measured both in the upper and lower limb with repeated contractions (Severijns, Lamers, Kerkhofs, & Feys, 2015), a sustained contraction (Kalron, Achiron, & Dvir, 2011) and after or during a functional activity (Sehle et al., 2011). A commonly used method is to calculate a fatigue index on the basis of a sustained contraction (Surakka et al., 2004). A fatigue index is based on the area under the force versus time curve during a contraction (Surakka et al., 2004). It has been demonstrated that these indexes during a 30 seconds of sustained contraction were more reliable in persons with MS than a repeated contraction (Djaldetti, Ziv, Achiron, & Melamed, 1996; Schwid et al., 1999; Surakka et al., 2004). This fatigue index determines the degree of motor fatigability of the muscle groups. There have been several studies that have measured motor fatigability in the upper limb in persons with MS (Ickmans et al., 2014; Severijns et al., 2015). It is not known if fatigability is a general concept or if it is muscle specific. There is only one study that indicates that static fatigue in one muscle correlates with static fatigue in other muscles (Schwid et al., 1999). As patients mainly suffer from fatigability, we wonder if there exists a generalizability of fatigability in the upper limb.

About 75% of individuals with MS show reduced unilateral of bilateral manual dexterity (Johansson et al., 2007; Ytterberg, Johansson, Andersson, Widen Holmqvist, & von Koch, 2008). This arm impairment impedes the ability to independently perform activities of daily living (ADL) and cause restrictions in use of the arms (Lamers et al., 2013). These impairments in ADL might be related to the abnormal decrease in strength over time. To our knowledge no study examined these association between these perceived difficulty to perform ADL and motor fatigability in persons with MS.

The purpose of this study is to examine motor fatigability in persons with MS on the basis of a static fatigue index. These results are compared with a control group. We additionally examine if the muscles of the upper limb show the same generalizability of muscle fatigue. As the arm has an important role in daily life, it is assumed that excessive muscle fatigue affect the use of the arm in daily life. Therefore the perceived difficulty to perform ADL will also be evaluated in both populations and this will be related to measures of fatigability in different joints.

3. Methods

3.1 Participants

In this cross-sectional study patients were recruited from existing databases in the Rehabilitation Research Centre (REVAL) and the Rehabilitation and MS centre Overpelt. Patients were included if they: (a) were diagnosed with MS according to McDonald criteria (McDonald et al., 2001), (b) were aged over 18, (c) did not experience any MS relapse in the past month, (d) did not have cognitive or mental problems that hinder participation in the study and (e) were right handed, as determined by the score on the Oldfield handedness inventory (Oldfield, 1971). The treating neurologist provided the score of the Expanded Disability Status Scale (EDSS) and the disease duration. Age- and sex-matched healthy controls were recruited through relatives, friends and acquaintances of the researchers. They were also excluded when they had orthopedic problems or problems that hinder the participation in the study. All participants gave their informed consent prior to participation. The ethics committees of UZ KU Leuven, Hasselt University and the Rehabilitation and MS Centre Overpelt, number B322201526676, approved the study on the 8th of December 2015

3.2 Procedure

3.2.1 Descriptive outcome measures

A set of clinical measurements and questionnaires were sampled to describe the level of functioning of the participants. A trained therapist performed these measurements. The motricity index (MI) was used to evaluate arm muscle strength (Croarkin, Danoff, & Barnes, 2004). Pinch grip, elbow flexion and shoulder abduction were measured and scored. Spasticity was assessed by the Modified Ashworth scale (MAS) (Bohannon & Smith, 1987). The MAS measured resistance during passive movement of the shoulder abductors, elbow flexors and wrist flexors. The Nine Hole Peg Test (NHPT) examined finger dexterity (Rosti-Otajarvi, Hamalainen, Koivisto, & Hokkanen, 2008). The time needed to place and remove nine pegs was recorded. Tremor was evaluated with the Fahn tremor rating scale (FTRS) (Hooper, Taylor, Pentland, & Whittle, 1998). This scale tested intention tremor, dysmetria and postural tremor. The Symbol digit modalities test (SDMT) was used to assess

information-processing speed (Drake et al., 2010). Cutaneous sensations of the thumb and index finger were measured with the Semmes Weinstein monofilaments test (SWMT) (Bell-Krotoski & Tomancik, 1987). Five monofilaments with different diameters were used to test tactile sensitivity in the fingertip of the thumb and the index finger. The participants were also asked to score a visual analogue scale (VAS) for baseline pain and fatigue over the last 24 hours before testing (McCaffery & Pasero, 1999). Finally patients were asked to fill out five questionnaires: three questionnaires for the impact and severity of fatigue (Modified fatigue impact scale (MFIS) (Kos et al., 2003), Neurological fatigue index for MS (NFI-MS) (Derksen et al., 2013) and Fatigue Severity scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989)), a questionnaire for anxiety and depression (Hospital anxiety and depression scale (HADS) (Zigmond & Snaith, 1983)) and the perceived difficulty to perform ADL (Manual Abilities Measure-36 (MAM-36) (Chen & Bode, 2010)).

3.2.2 Experimental design and outcome measures

The protocol started with a warm up of five minutes, consisting of general arm exercises. These exercises consisted of three series of ten repetitions, namely lifting the arms laterally and bending the arms to the chest. Then three maximal voluntary contractions and a 30 seconds sustained contraction were performed of the shoulder abductors, elbow flexors, handgrip and finger abductor. The strength of the shoulder abductors and the elbow flexors was assessed with the Biodex (Biodex Medical Systems, system 3, Inc, Shirley, New York, USA) (Drouin, Valovich-mcLeod, Shultz, Gansneder, & Perrin, 2004). The participants were assessed in a sitting position, with the arm flexed in 90 degrees for the elbow muscles, and in 45 degrees of abduction for the shoulder abductors. The trunk was also stabilized. The handgrip strength was evaluated with a digital Jamar handgrip device (E-Link Biometrics Ltd, Newport, UK) (Allen et al., 2011). These measurements were performed in a sitting position. The participants kept their arms along their body with the elbow bent and the wrist in a neutral position, according to the recommendations of the American Society of Hand Therapist (ASHT) (Trampisch, Franke, Jedamzik, Hinrichs, & Platen, 2012). A custom-made force sensor was used to determine the maximal finger abduction strength of the first index finger (van Duinen, Post, Vaartjes, Hoogduin, & Zijdewind, 2007). Therefore, the subjects had a force transducer in their hands. The bar of the force transducer was positioned parallel

to the index finger. By contracting the first dorsal interosseous muscle, the index finger exerted force to a bar. After this the signal was sent to a custom-made software program. Data were sampled with an analogue digital converter and stored on a laptop for further processing. During all the tests, the participants were verbally encouraged. First, there were three maximal contractions with an interval of 30 seconds asked. The highest of three contractions was used as the maximal voluntary contraction (MVC) for each muscle group. The static fatigue index (SFI) was calculated as described by Surakka et al. (Surakka et al., 2004). This index was based on the area under the force-versus-time curve (AUFC) for the entire contraction period from 0 tot 30 seconds. The AUFC during 30 seconds is divided by the hypothetical AUFC that would be obtained if the patient sustained maximal initial force during the whole 30 seconds. And this without any type of muscle fatigue (Figure 1).

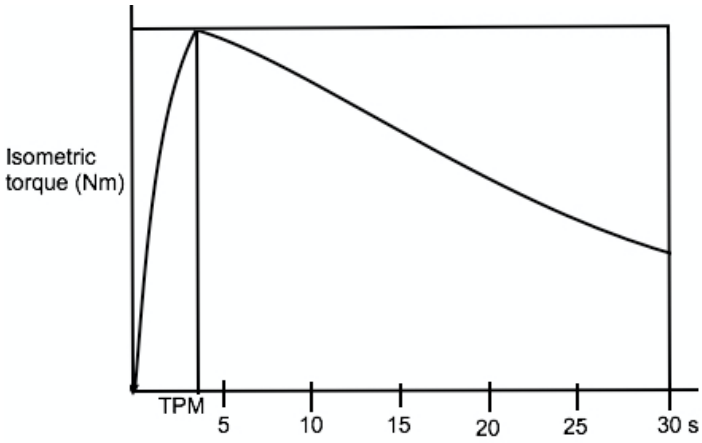

Figure 1: AUFC curve; hypothetical torque (Nm) versus time (s) curve during a sustained contraction for 30 s. During the period from 0 to 5, the highest value was set of the strength of the muscle group (TPM = time point of maximum value). The TPM serves as the starting point of the AUFC calculation.

3.3 Data-analysis

The SFI of the shoulder abductors, elbow flexors, handgrip and finger abductor was calculated in LabVIEW. All statistical analyses were performed in SAS JMP. Overall significance was set at $p < 0.05$. The SFI's of the different muscle groups were correlated to each other with a Pearson correlation coefficient. The SFI was compared between healthy controls and persons with MS with an unpaired t-test. The relation between arm performance and muscle fatigue was also evaluated with a Pearson correlation coefficient in the group of persons with MS.

4. Results

4.1 Participants

In total, 20 MS patients and 20 matched healthy controls participated in the study. Each group consisted of eight males and 12 females. The characteristics of the participants are detailed in table 1.

The majority of the MS patients were diagnosed with relapsing-remitting MS (70%), whereas 25% had secondary progressive MS and 5% had primary progressive MS. The mean EDSS score of the patients is 3.4 (range 1.5 – 6.5) and the mean disease duration is 16.3 years (range 3 – 37). This indicates that the MS patients rather had a moderate degree of disease stage.

Baseline, the VAS-scores showed a significant difference between the MS group and the healthy controls for fatigue ($p < 0.0001$), but not for pain. The tactile sensitivity was better in the healthy controls, both for the fingertip of the thumb ($p < 0.05$) and index finger ($p < 0.05$). The time to complete the NHPT was higher in the MS group ($p = 0.0019$), indicating on problems with manual dexterity. The mean time was 21.83 seconds and 17.07 seconds for the patients with MS and the healthy controls respectively. Muscle strength, evaluated with the MI, was significantly lower in the MS group than the healthy controls ($p < 0.005$). None of the persons with MS showed spasticity, measured by the MAS. Four MS patients had an intention tremor (20%) and two had a postural tremor (10%). The finger to nose test showed that the majority of the MS patients (60%) showed some degree of dysmetria.

Table 1. Subject characteristics

Variable	**pwMS**	**HC**	**p-value**
Age, years, mean (SD)	52.65 (9.16)	52.60 (9.24)	0.9864
Gender (M;F)	8;12	8;12	/
Type MS (RR;SP;PP)	14;5;1	/	/
Disease duration, years, mean (SD)	16.3 (9.45)	/	/
EDSS score, mean (SD)	3.40 (1.48)	/	/
VAS pain, mean (SD)	2.63 (2.69)	1.41 (2.09)	0.1168
VAS fatigue, mean (SD)	4.58 (2.55)	1.54 (1.25)	< 0.0001*
SDMT, mean (SD)	45.2 (10.71)	52.6 (8.99)	0.0233*
Monofilament thumb, mean (SD)	3.60 (1.27)	4.60 (0.60)	0.0037*
Monofilament finger 2, mean (SD)	3.50 (1.24)	4.90 (0.31)	< 0.0001*
NHPT, seconds, mean (SD)	21.83 (5.71)	17.07 (2.16)	0.0019*
MI (0-100), mean (SD)	93.05 (9.08)	100 (0)	0.0029*
Intention tremor, score (0;1;2;3;4)	16;4;0;0;0	19;1;0;0;0	/
Dysmetria, score (0;1;2;3;4)	8;11;1;0;0	20;0;0;0;0	/
Postural tremor, score (0;1;2;3;4)	18;2;0;0;0	20;0;0;0;0	/
MAM score, mean (SD)	66.88 (14.05)	89.73 (12.07)	< 0.0001*
HADS			
Anxiety, mean (SD)	6.45 (3.12)	3.05 (2.72)	0.0008*
Depression, mean (SD)	4.85 (3.18)	1.45 (2.19)	0.0004*

*p < 0.05; pwMS: patients with MS; HC: healthy control; SD: standard deviation; M: male; F: female; RR: relapsing remitting; SP: secondary progressive; PP: primary progressive; EDSS: Expanded Disability Status Scale; VAS: visual analogue scale; SDMT: symbol digit modalities test; NHPT: nine hole peg test; MI: motricity index; MAS: Modified ashworth scale; MAM: manual abilities measure; HADS: hospital anxiety and depression scale

4.2 Questionnaires

The three questionnaires about the impact and severity of fatigue demonstrated similar results (Table 2). According to the FSS cut-off score of four, none of the healthy controls were fatigued, while 13 of the persons with MS experienced fatigue during daily life. Persons with MS reported significantly more fatigue on the FSS than the healthy controls ($p < 0.0001$). According to the MFIS cut-off score of 38, also none of the healthy controls and 13 of the persons with MS were fatigued. So the persons with MS complained more of fatigue than the healthy controls ($p < 0.0001$). Additional, this questionnaire makes a distinction in three subdomains, namely a physical-, cognitive- and psychosocial scale. All these domains

showed a significant difference between the MS group and the healthy group ($p < 0.0001$). The NFI-MS has also three subdomains, namely a physical-, cognitive- and diurnal sleep scale. These three subdomains all indicated a significant difference between the groups ($p < 0.0001$).

The degree of anxiety and depression was assessed with the HADS. Here, it has been found that there was a significant difference between the persons with MS and the healthy controls. We can conclude that persons with MS had more anxiety ($p = 0.0008$) and exhibit higher levels of depression ($p = 0.0004$) than healthy persons.

The MAM demonstrated a significant difference between the groups ($p < 0.0001$) (Table 1). This indicated that persons with MS experience more problems by using the arms in daily life.

Table 2: Fatigue questionnaires of the MS patient and healthy controls

Variable	**pwMS**	**HC**	**p-value**
FSS			
Total, mean (SD)	4.61 (1.59)	2.26 (0.79)	< 0.0001*
Number of fatigued patients according to the cut-off score 4			
< 4	7	20	
> 4	13	0	
MFIS			
Total, mean (SD)	43.65 (16.78)	12.95 (12.23)	< 0.0001*
Fitness scale, mean (SD)	18.55 (8.10)	5.60 (5.66)	< 0.0001*
Cognitive scale, mean (SD)	20.60 (8.13)	6.40 (5.90)	< 0.0001*
Psychosocial scale, mean (SD)	4.50 (1.70)	0.95 (1.32)	< 0.0001*
Number of fatigued patients according to the cut-off score 38			
< 38	7	20	
> 38	13	0	
NFI-MS			
Total, mean (SD)	9.61 (3.30)	3.27 (3.42)	< 0.0001*
Physical scale, mean (SD)	13.43 (5.66)	4.15 (3.70)	< 0.0001*
Diurnal sleep scale, mean (SD)	9.39 (2.73)	3.56 (2.64)	< 0.0001*
Cognitive scale, mean (SD)	6.71 (3.06)	1.64 (2.16)	< 0.0001*

*p < 0.05; pwMS: persons with MS; HC: healthy controls; FSS: fatigue severity scale; MFIS: modified fatigue impact scale; NFI-MS: neurological fatigue index; SD: standard deviation

4.3 Motor fatigability

4.3.1 Maximal voluntary force (MVC)

The maximum of the three MVC's was calculated (Table 3 and Figure 2). The MVC values of the elbow flexors, handgrip and finger abductor were lower for persons with MS than the healthy controls, except for the shoulder abductors. Despite the fact that these were lower, there was no significant difference between the groups.

Table 3: Muscle strength for the muscle groups of persons with MS and healthy controls

Variable	**pwMS**	**HC**	**p-value**
MVC Shoulder, kg, (SD)	31.26 (14.98)	30.94 (10.30)	0.9387
MVC Elbow, kg, (SD)	38.31 (15.27)	43.86 (16.33)	0.2739
MVC Hand, kg, (SD)	36.95 (12.65)	38.90 (9.12)	0.5806
MVC Finger, kg, (SD)	27.87 (13.96)	33.67 (9.26)	0.0639

pwMS: persons with MS; HC: healthy controls; MVC: maximal voluntary contraction; kg: kilogram; SD: standard deviation

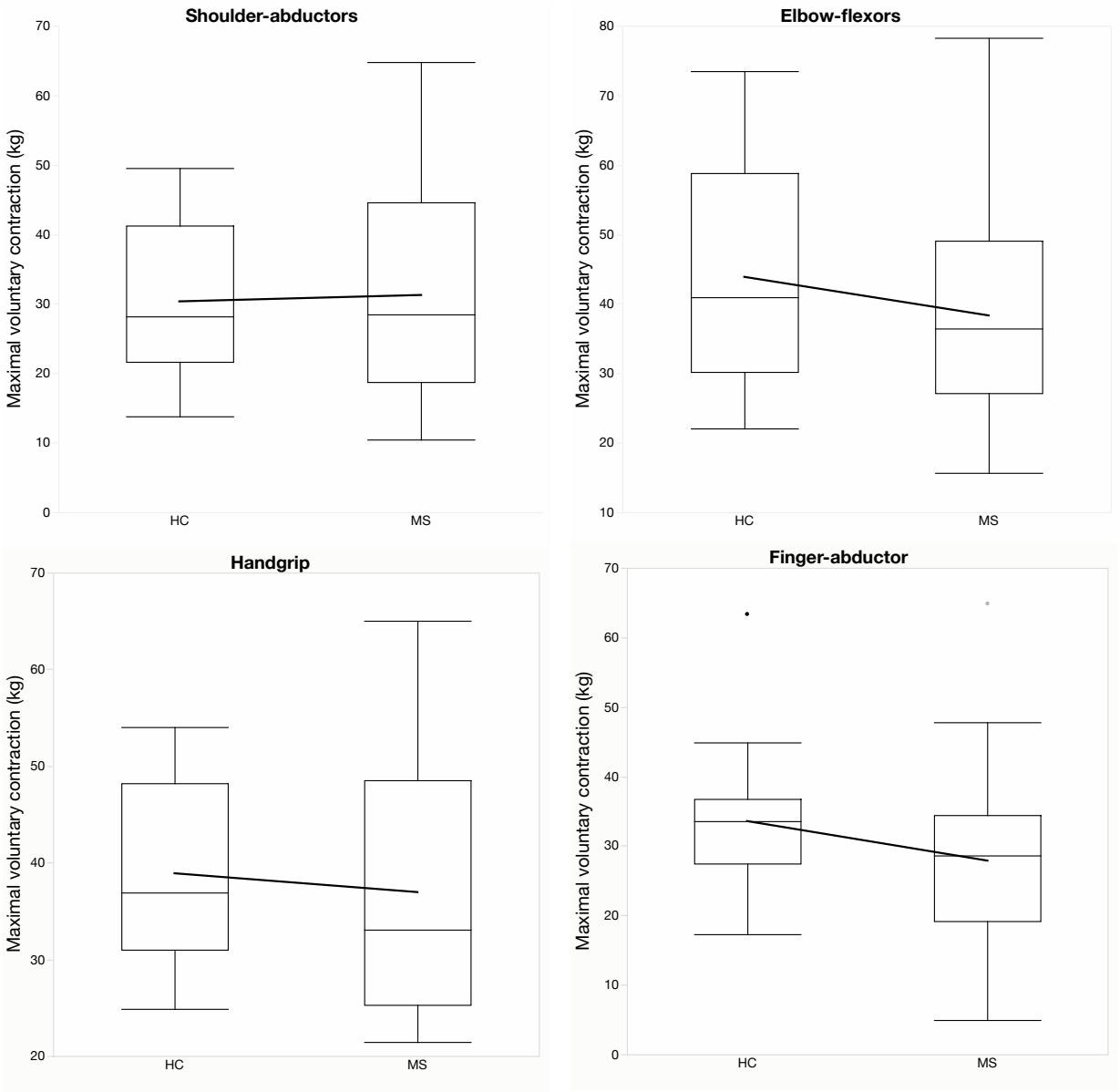

Fig 2: Box-plots of the maximal voluntary contractions in patients with multiple sclerosis (MS) and healthy controls (HC)

4.3.2 Static fatigue index (SFI)

The SFI's of the muscle groups are presented in table 4. The decline in strength over time is visualized in figure 3. The SFI for the elbow flexors was significantly higher in persons with MS (24%) versus healthy persons (17%) ($p = 0.0276$). The SFI for the shoulder abductors, handgrip and finger abductor were not significantly different between the groups.

Figure three shows clearly that there is no difference in motor fatigability of the shoulder-abductors, handgrip and finger abductor between persons with MS and healthy controls.

This can be seen in that the lines overlap largely. The elbow flexors do show a difference between the groups.

Table 4: Static fatigue indices of different muscle groups of persons with MS and healthy controls.

Variable	pwMS	HC	p-value
SFI Shoulder, %	42.12 (17.35)	40.42 (15.85)	0.8181
SFI Elbow, %	24.23 (11.27)	16.68 (9.47)	0.0276*
SFI Hand, %	30.33 (10.64)	26.42 (7.07)	0.1798
SFI Finger, %	28.15 (9.23)	26.63 (8.14)	0.583

*p < 0.05; pwMS: persons with MS; HC: healthy controls; SFI: static fatigue index

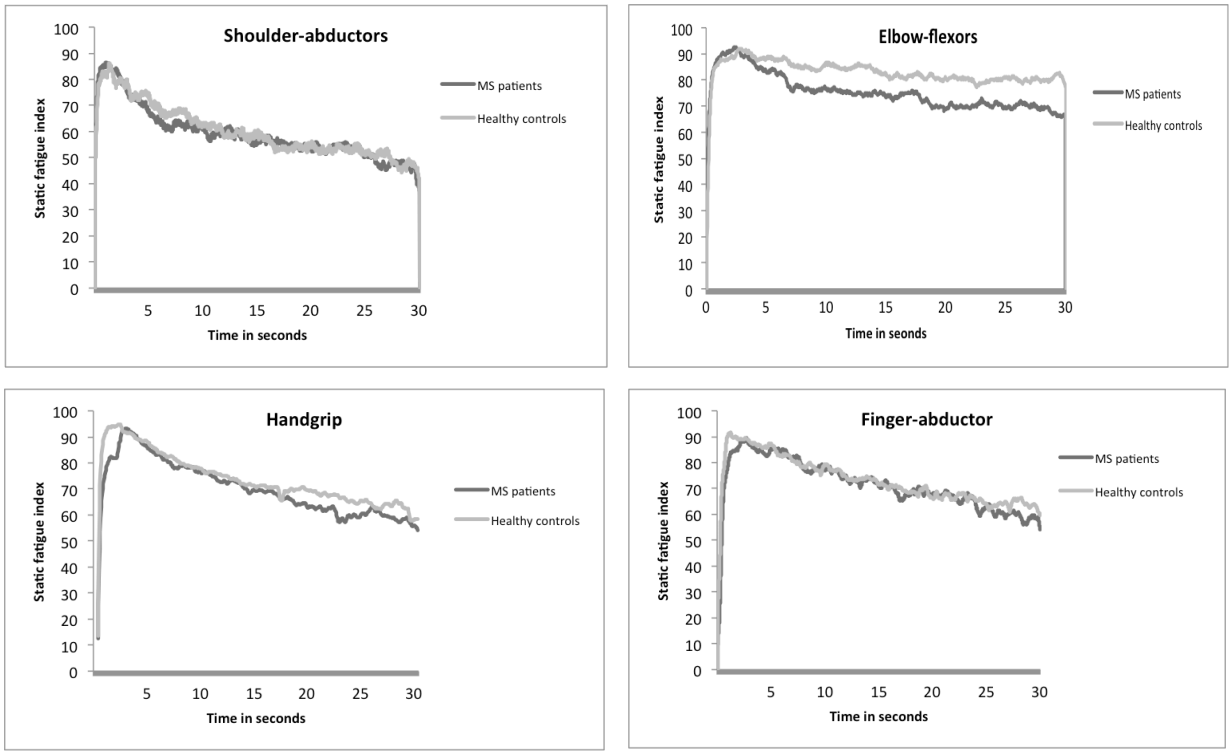

Fig 3: Static fatigue index (SFI) during a 30 seconds sustained contraction of the different muscle groups of patients with multiple sclerosis (MS) and healthy controls.

4.4 Correlations (Secondary questions)

4.4.1 Motor fatigability between the different muscle groups

The SFI of each muscle group was correlated with each other. The correlations have been analysed within the persons with MS and the healthy controls. The results are detailed in table 5. For the persons with MS, there was only one significant correlation between muscle fatigue of the shoulder abductors and elbow flexors (p = 0.0151). The other muscle groups showed no significant association.

Table 5: Correlation of the muscle groups on the basis of the static fatigue indexes of persons with MS and healthy controls.

Variable	**pwMS**		**HC**	
	Correlation	**p- value**	**Correlation**	**p-value**
SFI Shoulder - SFI Elbow	0.535	0.0151*	0.4241	0.0624
SFI Shoulder - SFI Hand	0.2749	0.2407	0.0647	0.7865
SFI Shoulder - SFI Finger	0.1106	0.6425	0.2977	0.2023
SFI Elbow - SFI Hand	0.3173	0.1728	0.3067	0.1884
SFI Elbow - SFI Finger	0.3544	0.1253	0.2832	0.2263
SFI Hand - SFI Finger	0.4548	0.4548	0.361	0.1179

*p < 0.05; pwMS: persons with MS; HC: healthy controls, SFI: static fatigue index

4.4.2 The relation of motor fatigability with maximal muscle strength

This association was only determined in persons with MS (Table 6). There was an association between the maximal strength and motor fatigability of the shoulder abductors (p = 0.0218). In the muscle group of the elbow flexors and the finger abductor, there was a trend toward significance between the strength and motor fatigability (p = 0.0908).

Table 6: Correlation between muscle fatigue and maximal strength of the different muscle groups in persons with MS

Variable	Correlation	p- value
MVC Shoulder - SFI Shoulder	-0.5095	0.0218*
MVC Elbow - SFI Elbow	-0.3882	0.0908
MVC Hand - SFI Hand	-0.0771	0.7466
MVC Finger - SFI Finger	0.4206	0.0648

*p < 0.05; SFI: static fatigue index; MVC: maximal voluntary contraction

4.4.3 Motor fatigability according to disease stage (EDSS score)

Motor fatigability of each muscle group was correlated with the EDSS score of the persons with MS. There was only one significant association between the finger abductor and the EDSS score (p = 0.0144) (Table 7). The correlation between the elbow flexors and disease stage tended toward significance (p = 0.0652).

Table 7: Correlation between the EDSS score and the static fatigue indexes of the muscle groups of persons with MS.

Variable	Correlation	p- value
EDSS - SFI Shoulder	0.0076	0.9746
EDSS - SFI Elbow	0.42	0.0652
EDSS - SFI Hand	0.2218	0.3473
EDSS - SFI Finger	0.5382	0.0144*

*p < 0.05; EDSS: Expanded Disability Status Scale; SFI: static fatigue index

4.4.4 The relation between motor fatigability and perceived difficulty to perform ADL

We also examined if motor fatigability affects the use of the arm in daily life. This was done by calculating the correlation coefficient between motor fatigability and the questionnaire 'MAM-36'. Table 8 showed that there was only one significant result for persons with MS. Motor fatigability of the elbow flexors was associated with the MAM-36 ($p = 0.0005$). The shoulder abductors tended toward significance ($p = 0.0801$).

Table 8: Correlation between arm performance (MAM-36) and static fatigue index of the muscle groups of persons with MS.

Variable	**Correlation**	**p- value**
MAM - SFI Shoulder	-0.4006	0.0801
MAM - SFI Elbow	-0.7033	0.0005*
MAM - SFI Hand	-0.2214	0.3482
MAM - SFI Finger	-0.1167	0.6241

*$p < 0.05$; MAM: Manual Abilities Measure; SFI: static fatigue index

5. Discussion

This study was designed to study possible differences in motor fatigability of the upper limb in persons with MS. Differences between persons with MS and healthy controls were investigated. Further it was examined whether there was a generalizability of motor fatigability in the different muscle groups and whether there was an association between motor fatigability and EDSS score, maximal strength and perceived difficulty to perform ADL. The main results of this study were that we could only detect higher fatigability in the elbow flexors in persons with MS. Only the fatigability of the finger abductor was significantly associated with the EDSS score. However, elbow fatigability was almost significantly related with the EDSS score, muscle strength and perceived difficulty to perform ADL. Additionally we could not detect a generalizability of motor fatigability in the muscles of the upper limb.

We found no difference in maximal strength between persons with MS and healthy controls. Only the maximal strength of the finger abductor tends toward significance between the groups. This indicates that both groups had about the same maximum strength in the upper muscles. This might be explained by the fact that the strength in the upper extremity muscles is relatively preserved compared to the lower extremity muscles in persons with MS. In lower extremity muscles, MS patients were significantly weaker than healthy controls (Schwid et al., 1999).

A contraction of 30 seconds is a common method to determine motor fatigability in the upper extremity (Djaldetti et al., 1996; Schwid et al., 1999; Severijns et al., 2015). All these sustained contractions were measured using the static fatigue index (SFI). This index has demonstrated reliability and validity for persons with MS (Schwid et al., 1999; Surakka et al., 2004) and has discriminative power to detect differences in motor fatigability (Surakka et al., 2004). Inspection of the curves (Figure 2) shows that fatigue is present in both groups, but the decline varied in both groups and in the different muscles.
The results of our evaluation using the SFI demonstrated that the index for the elbow flexors was significantly higher in persons with MS (24%) compared with healthy persons (17%). This means that persons with MS are not able to sustain their maximal strength as long as healthy controls. These findings are in line with a study that examined motor fatigability of

the elbow flexors and hip flexors in three groups. The results showed that the SFI was significantly higher in the group of MS patients as compared with patients with the chronic fatigue syndrome and healthy persons (Djaldetti et al., 1996).
The SFI of the handgrip was not significant. These results were in contrast with the findings of previous research. Two studies that investigated fatigability of the handgrip with sustained contractions of 30 seconds found a significant difference between persons with MS and healthy controls (Schwid et al., 1999; Severijns et al., 2015). We could possibly explain this on the basis of disease stage of persons with MS. In our study the EDSS scores varied from 1.5 to 6.5 (mean EDSS score 3.4), what a mild-to-moderate score is. Severijns et al. investigated fatigability of the handgrip in persons with MS with an EDSS score < 6 and with an EDSS score > 6 (Severijns et al., 2015). Schwid et al. also included more disabled persons with MS with a mean EDSS score of 5.5 (Schwid et al., 1999). Additional Severijns et al. found that persons with MS with EDSS scores > 6 showed significantly more fatigability during a sustained contraction of the hand compared with persons with MS with EDSS scores < 6 (Severijns et al., 2015). This may be due by the disease process or to other factors, such as disuse of the arms because of muscle weakness (Lamers et al., 2013). This may explain why we found in this group, with a rather mild-to-moderate EDSS score, no significant result for the handgrip fatigability. This is further supported by our finding of no significant relation between the SFI of the hand and the EDSS score. This is in contrast with the findings of the study of Severijns et al (Severijns et al., 2015). This may relate to the presence of more muscle weakness in persons with a higher degree of EDSS score.
We did find a correlation between SFI of the finger and a correlation that tends to significance of the elbow flexors and the EDSS score.

There was no generalizability of the same degree of motor fatigability in the muscle groups of the upper limb, both not in persons with MS and in healthy controls. There was only one correlation detected in the MS group, namely between the shoulder abductors and the elbow flexors. These two muscle groups showed a similar degree of motor fatigability. These findings are in contrast with these of Schwid et al. (Schwid et al., 1999). They found that static fatigue in one muscle correlated with static fatigue in other muscles. The study examined muscle groups in the upper and lower extremity. Additionally, there was no significant association between the SFI and the maximal baseline strength of the elbow

flexors, handgrip and finger abductor in persons with MS. These findings, of no correlation between maximal handgrip strength and muscle fatigue index, are in line with the findings of Severijns et al. and Schwid et al. (Schwid et al., 1999; Severijns et al., 2015), but in contrast with findings of previous research (Djaldetti et al., 1996; Iriarte & de Castro, 1998). Previous research showed associations between fatigability measures and baseline strength of the hand. The variations in results can be due to a different study population size, with the present study probably including a smaller group of persons with MS.

The last thing we examined was the relation between the SFI's and perceived difficulty to perform ADL in persons with MS. This was measured with the MAM-36 questionnaire (Chen & Bode, 2010). We found an association between the SFI of the elbow flexors and the MAM-36 score. So we can say that the elbow flexors impede activities of daily living of persons with MS. To our knowledge no further research examined this association. A study of Lamers et al. examined arm performance on the basis of clinical arm tests in wheelchair-bound MS persons. They found that MS persons moved both arms only half as much as a control group. These wheelchair-bound MS persons also described that they use their arms less frequently and with a lower quality of movement (Lamers et al., 2013). Further they also showed that these MS patients had lower handgrip strength and a higher score on the nine-hole peg test (NHPT) (Lamers et al., 2013). These last results are similar with the findings in our study. While these impairments hinder the activities of persons with MS in daily life, we cannot associate the decreased arm performance to motor fatigability.

5.1 Strengths and weaknesses

A strength of this study is that the whole protocol and the test were very standardized, so there could not be possible problems in administering the test. A second strength was that the measuring instruments (Biodex, Jamar Handgrip and Force tranducer) were all calibrated. A final strength is that two people carried out the data-analysis, the results were compared with each other and so there was less risk of potential errors.

The following weakness must be taken into account. The population size was rather low. In this study, only 20 MS patients were recruited. Ideally, the more patients you can include,

the more statistical power you can show in the study. However, the study of Schwid et al. recruited also only 20 persons with MS and these study found that the SFI of the handgrip was significantly higher in persons with MS. The elbow flexors were almost significantly higher in persons with MS (Schwid et al., 1999).

This study was based on two groups. One control group and one MS group with an EDSS score < 6. We believe that more information could be gathered by organizing a third group, namely a MS group with an EDSS score > 6. Patients with an EDSS score > 6 are more disabled and can lead to more pronounced differences between persons with MS, all with another degree of disability.
Secondly, it would be interesting for future research to take into account the recovery of muscle function post exercise. A delayed recovery can impede physical functions and activities in persons with MS (Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Petajan & White, 2000). Hence, it is interesting to examine recovery of the upper limb muscle function together with daily physical activity in patients with MS. This can make a very great contribution to the whole study.

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