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WENS, Inez & HANSEN, Dominique (2017) Muscle Strength, but Not Muscle Oxidative Capacity, Varies Between the Morning and the Afternoon in Patients with Multiple Sclerosis: A Pilot Study. In: AMERICAN JOURNAL OF PHYSICAL MEDICINE & REHABILITATION, 96 (11), p. 828-830.

DOI: 10.1097/PHM.0000000000000703
Handle: http://hdl.handle.net/1942/23127

Muscle strength, but not muscle oxidative capacity, varies between the morning and the afternoon in patients with multiple sclerosis: a pilot study

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Abstract

Objective

Despite frequent muscle strength or muscle oxidative capacity (based on exercise-onset oxygen uptake (VO_2) kinetics) assessments in patients with multiple sclerosis (pwMS), the impact of time of day on these parameters is often not taken into account. Based on observations in healthy subjects, it remains to be studied whether muscle strength, and/or exercise-onset VO_2 kinetics, varies between the morning and the afternoon in pwMS.

Design

In this prospective observational pilot study walking capacity, exercise-onset VO_2 kinetics, isometric knee extension/flexion strength (dynamometry), and self-reported fatigue (SRF) were measured in 11 pwMS (age 51.8±9.3 years, body mass index 24.7±5.1 kg/m², EDSS 3.5±1.4, 3 males) in the morning and five hours later (afternoon).

Results

In the afternoon SRF (1.9±0.9cm) and muscle strength (knee extension peak torque at 45°: 84±26Nm) were significantly lower ($p<0.05$), than in the morning (SRF: 1.2±0.9cm, knee extension peak torque at 45°: 93±32Nm), but walking capacity and exercise-onset VO_2 kinetics were similar at these two time points ($p>0.05$).

Conclusions

Consistent with observations in healthy subjects, muscle strength varies between the morning and the afternoon in pwMS, under the conditions of the present study. These findings suggest that muscle strength assessments should be conducted at similar or nearly similar times of the day in order to minimize diurnal variation in these measures and hence insure correct interpretation.

Keywords: multiple sclerosis, muscle strength, muscle oxidative capacity, time of day

Introduction

During the last few decades patients with MS (pwMS) have been referred to rehabilitation centers for treatment often involving exercise interventions and/or more studies on the impact of exercise intervention in pwMS are have been reported. During these exercise interventions and experimental studies muscle strength and muscle oxidative capacity are often measured.[1,2]

It remains an important but yet unresolved issue whether muscle strength or muscle oxidative capacity varies during the day in pwMS. In healthy individuals, it already has been shown that muscle strength,[3] but not exercise-onset oxygen uptake (VO_2) kinetics (as a validated noninvasive marker for muscle oxidative capacity),[4] varies during the day.

Since it is unclear whether these circadian variations can also be seen in MS patients, this study aims to determine muscle strength and muscle oxidative capacity at different time points during the day (during the morning and the afternoon). This will be of significant importance to the standardization of physical fitness assessment methodology. Moreover, if circadian variations are demonstrated in PwMS, care must be taken to insure that repeated exercise testing is conducted at the same time of day as the initial testing.

Materials and methods

Subjects

Eleven ambulatory patients with MS (pwMS, 6 with relapsing remitting MS and 5 with progressive MS), diagnosed for at least 12 months (clinically stable for at least 6 months) ahead of study and free from cardiovascular, renal or pulmonary disease (aged 30-70 years), agreed to participate in this study. Signed informed consents were obtained from all subjects, and the author's institutional review board (Jessa Hospital Hasselt and Hasselt University, Belgium) approved the study. Sample size was based on an a priori power calculation (paired comparisons, $p<0.05$, two-tailed, statistical power $\alpha \geq 0.95$) by data from Racinais et al.[3]. Based on this calculation ≥7 pwMS had to be included in the study to achieve appropriate power.

Study design

This was a prospective study with repeated measurements (Figure 1). In the morning (between 8.30-10.30 AM) and five hours later (afternoon) fatigue was scored by the patient, followed by two subsequent low-to-moderate-intensity endurance exercise sessions (for assessment of exercise-onset VO_2 kinetics), 2-min walking test, and dynamometry test. Participants were not allowed to smoke or to use caffeine before the first test and between the first and second test. Subjects were allowed to eat something of choice ahead of exercise testing in order to replicate clinical practice. Furthermore, they were instructed to remain sedentary between the first and the second test, to avoid physical activity induced fatigue.

Fatigue

Subjects were advised not to perform any exercise the day before or on the day of testing. After assessment of body weight and height, with calculation of body mass index (BMI) and a clinical assessment, performed by a neurologist, to determine the expanded disability status scale (EDSS – to quantify disability in pwMS), self-reported fatigue (SRF) was assessed by the Rochester's Fatigue Diary, which was administered immediately before the first exercise test.[5]

Muscle oxidative capacity

Methodologies used to indirectly assess muscle oxidative capacity have been previously described.[2] Subjects performed a submaximal cardiopulmonary exercise test on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany). Pulmonary gases were continuously assessed breath-by-breath using a mass spectrometer and volume turbine system (Jaeger Oxycon, Erich Jaeger GmbH, Germany). During the exercise test, oxygen uptake (VO_2, ml/min) and expiratory volume (VE, l/min) were assessed breath-by-breath, after which these data were averaged every 10 seconds. Heart rate was continuously monitored by 12-lead ECG device and averaged during the last minute of the exercise bout. At the end of each exercise bout ratings of perceived exertion (RPE) were reported by the subject on a 6-20 Borg scale. Subjects were seated on bike for three minutes to obtain resting data. Next, subjects were instructed to cycle at a rate of 70 rpm, against a resistance corresponding to 25% of predicted cycling power output (W_{max}, based on age, gender, body height and weight)[6], for six minutes. After six minutes of cycling subjects remained seated on bike for an additional six minutes, after which a second 6-minute exercise bout at an identical workload was carried out.

Exercise-onset VO_2 kinetics were calculated algebraically and expressed as mean response time (MRT).[7] Resting VO_2 was taken as the VO_2 during the final minute before exercise began. Steady-state VO_2 was defined as the averaged value between the fifth and sixth minute of cycling. The difference between the rest VO_2 and steady-state VO_2, multiplied by exercise time (six minutes), was defined as the expected amount of O_2 consumed during the entire exercise bout. However, in order to examine skeletal muscle oxidative capacity by calculating exercise-onset VO_2 kinetics, it is important to ignore the cardiodynamic phase of the kinetics. As a result, the first 20 seconds of data after onset of exercise were eliminated.[8] The sum of VO_2 above resting level was defined as the actually achieved VO_2 during the entire exercise bout. The oxygen deficit could then be calculated by: expected amount of VO_2 – actually achieved VO_2. Division of this oxygen deficit by the difference between rest VO_2 and steady-state VO_2 equals MRT. The resultant MRT, multiplied by 60, finally produced a value expressed in seconds, and this outcome is used throughout this manuscript to quantify exercise-onset VO_2 kinetics. Finally, the two MRT's that were obtained from the two exercise bouts were averaged. Exercise-onset VO_2 kinetics are faster in skeletal muscle with predominantly slow-twitch fibers, and/or with increased activation of oxidative muscle enzymes, and slowed in pwMS[2,9-10], and are improved by exercise training.[11] It is therefore accepted that assessing exercise-onset VO_2 kinetics is a sensitive tool for the specific evaluation of oxidative capacity of skeletal muscle.[12]

Walking capacity

Subjects were instructed to walk as far as they could within a 2-min period, in accordance to previous methodology.[13] Subjects walked at maximal effort, back and forth in a 30-meter hallway, and were permitted to use their habitual assistive devices. Immediately after termination of the test, the total walking distance and RPE were recorded.

Muscle strength

Maximal voluntary knee-extensor and flexor strength of both legs was measured unilaterally using an isokinetic dynamometer (Biodex Medical Systems®, Shirley, New York, USA). Methodologies for the assessment of muscle strength have been previously described.[1] Two maximal isometric knee-extensions and flexions (4 seconds) at knee angle of 45° and 90° were performed. The highest isometric extension torque (Nm) of the manually smoothed curves at this knee angle was selected as maximal isometric torque. Data from the two legs were averaged.

Statistical analysis

All calculations were performed using the Statistical Package for the Social Sciences v. 22.0 (SPSS®). Data were expressed as means±SD. Shapiro-Wilk tests confirmed normal distribution of data. To compare parameters in morning vs. afternoon, paired sample t-tests were used. Univariate relationships between parameters were examined by Pearson correlations. Statistical significance was set at $p<0.05$ (2-tailed).

Results

Eleven pwMS participated in this study (age 51.8±9.3 years, body mass index 24.7±5.1 kg/m^2, EDSS 3.5±1.4, gender: 8 females and 3 males).

Outcomes in morning vs. afternoon are displayed in Table 1. Outcomes of SRF, Borg RPE during walking, knee extension and knee flexion (at 90° only) strength testing, performed in the afternoon were significantly lower than those collected in the morning ($p<0.05$). Trends for differences between time points were found for Borg RPE during the cycling test ($p=0.06$).

SRF measurements during the day did not correlate with MRT, walking capacity or muscle strength ($p>0.05$).

Discussion

Data from the present study confirm, as observed in healthy individuals, that maximal muscle strength varies significantly between the morning and the afternoon in pwMS, while muscle oxidative capacity (based on exercise-onset VO_2 kinetics) does not. For example, maximal knee extension strength at 45° flexion decreased from 93±32Nm to 84±26Nm ($p<0.05$), while MRT (quantifying parameter for exercise-onset VO_2 kinetics) remained stable ($p=0.25$), during the day. In addition, self-reported fatigue levels were significantly greater in the afternoon (SRF=1.9±0.9cm) vs. morning (SRF=1.2±0.9cm, $p<0.05$). Even though walking capacity did not vary between the morning and the afternoon in pwMS, perception of exertion at these similar workloads (Borg RPE scores) was higher in the afternoon (12.3±2.6) than in the morning (10.6±2.0, $p<0.05$) . It thus follows that when evaluating pwMS, timing of muscle strength assessment should be standardized rigorously to properly evaluate these changes at follow-up. On the other hand, such standardization does not seem to be necessary when assessing changes in walking distance and MRT during follow-up. These findings therefore are of significant importance to physical fitness assessment methodology used in pwMS. It is uncertain whether such timing standardization was employed during strength tests in previous studies examining pwMS.

In healthy individuals, it is speculated that variations in muscle strength during the day are related to diurnal fluctuations in central nervous system command and contractile state of muscles.[3] This may be the case in pwMS as well.

The present study has some limitations, resulting in recommendations for future research. Given the explorative nature of the study, we used a small sample size (although sufficient based on *a priori* sample size calculation). Larger sample sizes are needed to confirm our findings. Furthermore, the fatigue scale used in the present study has not been specifically validated for pwMS. Finally, participants were allowed to eat and drink something of choice before and between exercise tests in order to replicate clinical practice. Since these interventions might modify the physiological profile of a person, it is recommended that subjects consume a standardized diet before the morning testing session and during the interval between the morning and the afternoon testing sessions.

In conclusion, under the conditions of the present study, muscle strength, but not muscle oxidative capacity, varies significantly between the morning and the afternoon in pwMS. These findings suggest that care should be taken to insure that repeated measurements of strength should be taken at approximately the same time of day in pwMS.

Conflict of Interest Statement

None declared.

Funding

None.

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