Multiple Sclerosis and Related Disorders 70 (2023) 104479

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

The increased perceived exertion during the six minute walking test is not accompanied by changes in cost of walking, gait characteristics or muscle fatigue in persons with multiple sclerosis

Kyra Theunissen [a,b,c,*], Guy Plasqui [a], Annelies Boonen [b], Annick Timmermans [c], Pieter Meyns [c,d], Peter Feys [c,d], Kenneth Meijer [a]

[a] *Department of Nutrition and Movement Sciences, School of Nutrition and Translational Research in Metabolism, Maastricht University, The Netherlands*
[b] *Department of Internal Medicine, Division of Rheumatology, Maastricht Universitair Medisch Centrum, and Care and Public Health Research Institute, The Netherlands*
[c] *REVAL Rehabilitation Research Center, REVAL, Faculty of Rehabilitation Sciences, Hasselt University, Belgium*
[d] *Universitair MS Centrum Hasselt-Pelt, UMSC, Belgium*

ARTICLE INFO

Keywords:
Multiple sclerosis
Cost of walking
Gait
Energy metabolism
Muscle fatigue
Fatigue

ABSTRACT

Background: Persons with Multiple Sclerosis (pwMS) frequently experience walking difficulties, often expressed as a slower walking speed during the 6 Minute Walking Test (6MWT). In addition, slower walking speeds are also related to higher levels of perceived exertion. PwMS are also known to have a higher energetic Cost of walking (Cw) and may experience muscle fatigue during prolonged walking. In this study, we aimed to explore changes in Rate of Perceived Exertion (RPE) and the Cw within participants during the 6MWT in pwMS. Additionally, concomitant changes in the mean and variability of gait characteristics and changes in muscle activation describing muscle fatigue were assessed.

Methods: The 6MWT was performed on an instrumented treadmill while three-dimensional motion capture and gas exchange were measured continuously. RPE on the 6–20 borg-scale was questioned directly before and after the 6MWT. Cost of walking was expressed in Joules/kg/m. Muscle fatigue was assessed by increases in Root Median Square (RMdS) and decreases in Median Frequency (MF) of the recorded EMGs. Wilcoxon-Signed Rank test was used to assess a difference in RPE before and after the 6MWT. Linear mixed models, while controlling for walking speed, were used to assess changes in Cw, mean and variability of gait characteristics and RMdS and MF of muscle activation.

Results: 28 pwMS (23 females, mean ± standard deviation age 46 ± 10 years, height 1.69 ± 0.08 meter, weight 76 ± 18 kilogram, EDSS 2.7 ± 1.3) were included. Although the RPE increased from 8 to 12, no changes in Cw were found. Walking speed was the only spatiotemporal parameter which increased during the 6MWT and RMdS of the gastrocnemius and tibialis anterior muscles increased. The soleus muscle decreased in MF over time.

Conclusion: The increases in RPE and walking speed was not accompanied by a change in Cw during the 6MWT which indicates that the perceived exertion was not accompanied by an increased physical exertion. Changes in muscle activation might give an indication for muscle fatigue but were inconclusive. Although the 6MWT reflects daily life walking challenges for pwMS, this test did not show the expected changes in gait parameters in our sample.

1. Introduction

Multiple Sclerosis (MS) is a neurodegenerative autoimmune disease which causes demyelination of the CNS and axonal damage, leading to physical impairments. The most important physical activity, reported by persons with MS (pwMS) is walking and is affected from an early stage of MS. (Heesen et al., 2018) Limitations in walking ability have been repeatedly associated with (self-reported) perceived fatigue and decreased daily physical activity. (Kalron, 2015) On the longer term, decreased physical fitness is associated with increased risk for co-morbidities such as cardiovascular impairments and depression. (Dalgas et al., 2019) Maintaining walking ability is therefore an

* Corresponding author.
E-mail address: kyra.theunissen@maastrichtuniversity.nl (K. Theunissen).

https://doi.org/10.1016/j.msard.2022.104479
Received 8 November 2022; Received in revised form 7 December 2022; Accepted 22 December 2022
Available online 23 December 2022

important goal in rehabilitation for pwMS.

In clinical settings, walking ability is generally evaluated by the 6 Min Walking Test (6MWT). (Stella et al., 2020; Comber et al., 2017) Impaired walking ability has been characterized in several studies by slower walking speeds during the 6MWT in pwMS. (Comber et al., 2017; Savci et al., 2005; Goldman et al., 2008) In addition, slower walking speeds are related to increased levels of both perceived psychological and physical fatigue assessed with the Modified Fatigue Impact Scale (MFIS). (Goldman et al., 2008) In our study, perceived exertion is referred to as a self-reported subjective sensation of perceived exertion by the Rating of Perceived Exertion (RPE) on the 6–20 point borg-scale. Physical exertion is referred to as an objective decline in performance during a specific task. Recent studies have observed a decline of ≥10–15% in walking speed between the first and last minute of the 6MWT in about half of pwMS with moderate-to-severe disability, referred to as walking fatigability. (Van Geel et al., 2020; Leone et al., 2016) It is unknown whether changes in walking speed are also accompanied by a change in the metabolic energy demand during the 6MWT. Physical exertion might be addressed more comprehensive by simultaneously assessing the change in walking speed and the metabolic energy demand during the 6MWT.

Metabolic energy demand during walking is typically expressed as the energetic Cost of walking (Cw) which indicates the amount of energy consumed per distance walked and is expressed in Joules per kilogram bodyweight per meter ($J \cdot kg^{-1} \cdot m^{-1}$). Persons with MS walk at a greater Cw compared to healthy persons (Stella et al., 2020) but with a similar optimal speed, as described by the U-shaped relationship between walking speed and the Cw. (Theunissen et al., 2021) Since walking is energetically more demanding in pwMS, an increased Cw might be accompanied by changes in gait parameters. Evaluating this simultaneously will contribute to the understanding of both physical and perceived fatigue. PwMS are known to walk at a lower cadence, shorter step length and wider step width, compared to healthy persons. (Comber et al., 2017) Furthermore, within-subject variability of these gait characteristics is also increased in pwMS. (Arpan et al., 2020) Considering that these are all predictors for the Cw, an increased metabolic effort could be accompanied by alterations in these parameters. (Donelan et al., 2001; Donelan et al., 2002) In addition, Eken et al. (Eken et al., 2020) pointed to the relevance of measuring muscle fatigue during walking in pwMS and showed a worsening of muscle fatigue irrespective of walking speed. Considering muscle activation as the primary source of metabolic energy demand during walking, altered activation strategies and muscle fatigue can be related to an increased Cw. (Rudroff et al., 2014; Ng et al., 2004)

In this study, we aimed to explore changes in RPE and the Cw within participants during the 6MWT in pwMS. Additionally, concomitant changes in the mean and variability of gait characteristics and changes in muscle activation reflecting muscle fatigue were assessed.

2. Materials and methods

This study employed an observational experimental design among pwMS. Participants were recruited from the MS Rehabilitation Center (Overpelt, Belgium) and Zuyderland Hospital (Sittard-Geleen, the Netherlands) between 24/04/2019 and 01/02/2021. All participants received verbal instructions and gave written informed consent. The study was approved by Medical Ethics Committee of Maastricht University Medical Center NL67805.068.18 and conducted in compliance with the Declaration of Helsinki. A detailed experimental set-up and sample size calculation is provided in Supplementary File 1.

2.1. Participants

PwMS were eligible for inclusion if they were between 18 and 65 years old, able to walk for 6 min without walking aid, expressed as an Expanded Disability Status Scale (EDSS) ≤5.5. Exclusion criteria were: relapse < 3 months- and botulinum toxin treatment in lower limb < 6 months prior to measurements, contraindication for physical activity, fractures or other comorbidities that could influence gait or energy metabolism.

2.2. Experimental set-up

All participants were instructed to avoid vigorous physical activity <24 h and eating and drinking (with the exception of water) <3 h prior to the measurement. First, Resting Metabolic Rate (RMR) was measured via indirect calorimetry by collecting consumed oxygen (O2) and produced Carbon Dioxide (CO2) (Omnical, Maastricht Instruments, Maastricht The Netherlands). (Schoffelen and Plasqui, 2018) Participants were positioned under a ventilated hood in a supine position for 35 min while watching a calming nature documentary.

Bi-lateral electromyography (EMG) of 3 main lower limb muscles (gastrocnemius medialis (GM), soleus (SOL), tibialis anterior (TA)) susceptible to fatigue during walking (van der Krogt et al., 2012) and known to affect gait in pwMS (Kempen et al., 2016) were measured via 6 surface electrodes (1000 Hz, Trigno Wireless, DelSys Inc, USA). The skin was shaved and rinsed with pure alcohol before electrodes were attached following the SENIAM guidelines [17]. Consequently, subjects laid down and relaxed for several minutes to identify baseline noise in muscle activity.

The 6MWT was performed at the Computer Assisted Rehabilitation Environment (CAREN) system (Motek Medical B.V., Amsterdam, The Netherlands) consisting of a six degrees-of-freedom motion base with a dual belt treadmill and integrated force plates. The 180° cylindrical screen projected a static virtual environment. Motion capture system consisted of 12 real-time infrared cameras (Vicon Motion Systems, Oxford, United Kingdom) enabling the tracking of reflective markers. To guarantee reliability of marker placement, a single researcher attached the markers to the participants' skin with adhesive tape according to the Human Body Model v2 Lower Limb. (van den Bogert et al., 2013) All participants wore similar gym shoes of appropriate size to avoid influence from insoles and an upper body safety harness attached to an overhead suspension system to prevent injury in case the subject would lose balance.

To familiarize with treadmill walking prior to the 6MWT, all participants completed 2 walking bouts of 3 min at a leisurely self-paced mode. This self-paced algorithm adjusts the treadmill speed in accordance with the position of the subject on the treadmill. (Sloot et al., 2014) After resting time to limit fatigue due the familiarization bouts, the subjects were instructed to walk as fast as possible during the 6MWT (ATS Statement 2002) and data collection started after participants indicated to have reached their starting pace to avoid delay of treadmill acceleration. During the 6MWT, participants wore a face mask continuously collecting respiratory gasses. RPE on a 6–20 point borg-scale (Borg, 1970) before and directly after the 6MWT and physical exertion was assessed by continuously monitoring heart rate via a chest strap (Polar H9).

Before the 6MWT, the following questionnaires were completed to characterize the population: Modified Fatigue Impact Scale (MFIS;range 0–84) for assessing the impact of fatigue on daily life in which a score >38 indicates MS-related fatigue, (Flachenecker et al., 2002) Fatigue Severity Scale (FSS;range 1 – 7) with a score ≥4.6 indicating MS-related fatigue, (Flachenecker et al., 2002) MS Walking Scale-12 (MSWS-12; range 0–100) with a score between 25 and 49 indicating moderate disability and ≥50 a substantial loss of functional independence. (Goldman et al., 2017)

After the experiment, participants' body composition was measured by assessing total body water via deuterium labeled water. (Westerterp et al., 1995) Fat Free Mass (FFM) was calculated from total body water. (Van Marken Lichtenbelt et al., 1994)

2.3. Data processing

Determination of initial contact was based on vertical ground reaction forces and marker data. (Zeni et al., 2008) Gait characteristics contributing to the Cw (Donelan et al., 2001; Donelan et al., 2002) and included in the analysis were: walking speed, cadence, step length and step width. Within-subject variability was described by the coefficient of variation as the ratio of the standard deviation to the mean and expressed in percentage.

Resting metabolism was expressed in Joules/kilograms body mass/minute ($J\bullet kg^{-1}\bullet min^{-1}$). Steady state net Cw was derived by subtracting resting metabolism from steady state energy expenditure (minute 3,4,5 and 6) expressed in Joules/kilograms body mass/distance walked per minute in meters ($J\bullet kg^{-1}\bullet m^{-1}$).

All recorded EMG signals were visually inspected and included for further analysis in case clear bursts were visible. Signals were excluded in case the Signal to Noise Ratio (SNR) was <5. All above mentioned parameters were processed via a custom made Matlab script (MathWorks, USA).

2.4. Statistical analysis

All statistical analyses were performed using SPSS Version 25 (IBM, Chicago, IL). Demographic and clinical characteristics were reported in means±standard deviations. Normal distribution was assessed with the Shapiro-Wilk test. The RPE before and after the 6MWT was statistically compared by the Wilcoxon Signed-Rank Test.

Linear mixed models were used to assess whether the Cw, gait characteristics (walking speed, cadence, step length, step width) and muscle activation changed between minutes of the 6MWT. Main effects were assessed as fixed effects with time as a factor. Walking speed was included as a covariate in case of either a linear or polynomial relationship. Consequently, model accuracy was determined for every outcome measure independently, assessing the Schwarz's Bayesian Criterion (BIC) for selecting the covariance type. Multiple comparisons over time were adjusted with Least Significant Difference (LSD). Muscle fatigue was defined as a concomitant increase over time in the signal amplitude as Root Median Square (RMdS) and a decrease in the spectral frequencies as Median Frequency (MF). (De Luca, 1984)

3. Results

Thirty-two participants were measured of which data of four persons were not included due to technical errors ($n = 2$) and belated notification of comorbidities affecting gait as an exclusion criteria ($n = 2$). The population mean was mildly disabled with a mean EDSS of 2.67 (range 1–5.5). Forty-four percent (%) of the pwMS reported an impact of fatigue on daily life, 59% reported fatigue, 37% moderate walking impairment and 26% substantial loss of functional independence, on the MFIS, FSS and MSWS-12, respectively. All mean±SD descriptive subject parameters are reported in Table 1.

Table 1
Descriptive parameters for all pwMS.

Parameter	(n = 28) Mean ± SD
Gender (male/female)	5/23
Age (years)	46 ± 10
Height (meters)	1.69 ± 0.08
Weight (kilograms)	76 ± 18
Fat Free Mass (%)	32 ± 10
Resting Metabolic Rate (ml $O2\cdot kg^{-1}\cdot min^{-1}$)	2.92 ± 0.39
EDSS	2.67 ± 1.29
Time since diagnosis (years)	11 ± 6
Type of MS (rr/pp/sp/ns)	20/3/1/4
Modified Fatigue Impact Score	42 ± 22
[redacted]score >38:% (n)	44% (12)
Fatigue Severity Scale	4.67 ± 1.17
[redacted]score >4.6:% (n)	59% (16)
MS Walking Scale-12	34 ± 27
[redacted]score 25–49:% (n)	37% (10)
[redacted]score ≥50:% (n)	26% (7)
Total 6MWD (meters)	486 ± 129

Abbreviations: PwMS= persons with Multiple Sclerosis; RMR= resting metabolic rate in ml $O2\cdot kg^{-1}\cdot min^{-1}$; EDSS= Expanded Disease Disability Scale; rr=relapsing remitting; pp= primary progressive; sp= secondary progressive, ns= not specified; 6MWD= six minute walking distance.

3.1. Changes in rpe and cw

After the 6MWT the average RPE significantly increased from 8 ± 2 to 12±3 (z=−4.475,p=<0.001). The mean Cw per minute is presented in Fig. 1 and all gait parameters interest are reported in Table 2. Linear mixed models with walking speed as polynomial covariate revealed no change in Cw over time ($F = 2.365, p = .097$). Heart rate increased from the 1st to the last minute of the 6MWT with 15% from 101 to 118 beats per minute.

3.2. Changes in gait characteristics

Fig. 1 presents the walking speed per minute during the 6MWT. This was the only gait characteristic that changed over time during the 6MWT (F = 7.331,p<.001) and increased gradually from 1.33 to 1.44 m/s. Post-hoc comparison mainly showed differences between the first and second half of the 6MWT with an increase between minute 1 and all the following minutes as well as between minute 2 and minutes 4,5,6. Finally minute 3 showed a slower walking speed, compared to minutes 5 and 6. Cadence, step length and step width (adjusted for walking speed as polynomial covariate) did not change over time (F = 0.464,p=.799;F = 1.949,p=.094;F = 0.471,p=.797, respectively). Within-subject variability in walking speed, cadence, step length and step width did not change over time ($F = 23.446, p = .082; F = 26.211, p = .518; F = 25.991, p = .084; F = 24.642, p = .766$, respectively).

3.3. Changes in muscle activation

In total five participants were excluded from EMG analyses due to technical errors. The GM, SOL and TIB from three participants were excluded due to no clear bursts visible. Additionally, one minute of the GM was excluded due to a SNR<5. The mean±sd SNR of the GM, SOL and TIB were 67±76, 39±50 and 31±16, respectively. Fig. 2

The GM showed an increase in RMdS over time (F = 3.012,p=.017) with a significant linear effect of walking speed (F = 37.250,p=<0.001). Post-hoc comparison showed differences between minute 1 and minutes 2 and 3 and between minute 5 and 6. However, MF of the GM did not change over time (F = 1.144,p=.346). The SOL showed no increase in RMdS over time (F = 1.587,p=.175). There was a significant decrease over time in MF (F = 3.956,p=.003) between minutes 1 and 2 and minutes 3,4,5,6. The TA muscle showed a significant increase in RMdS over time (F = 2.482,p=.038) with a main effect of walking speed (F = 23.432,p=<0.001). Post-hoc comparison showed a difference between minutes 3 and 4, compared to minute 5. However, the TA showed no change in MF over time (F = 2.270,p=.057).

4. Discussion

This is the first study that explored changes in RPE and the Cw within participants during the 6MWT in pwMS. Additionally, concomitant changes in the mean and variability of gait characteristics and changes in muscle activation describing muscle fatigue were assessed. We observed no significant changes in Cw during the 6MWT while a 4 point increase in RPE was found. This indicates that the increased perceived exertion was not accompanied by an increase in physical exertion.

The increased RPE during the 6MWT is in line with other studies

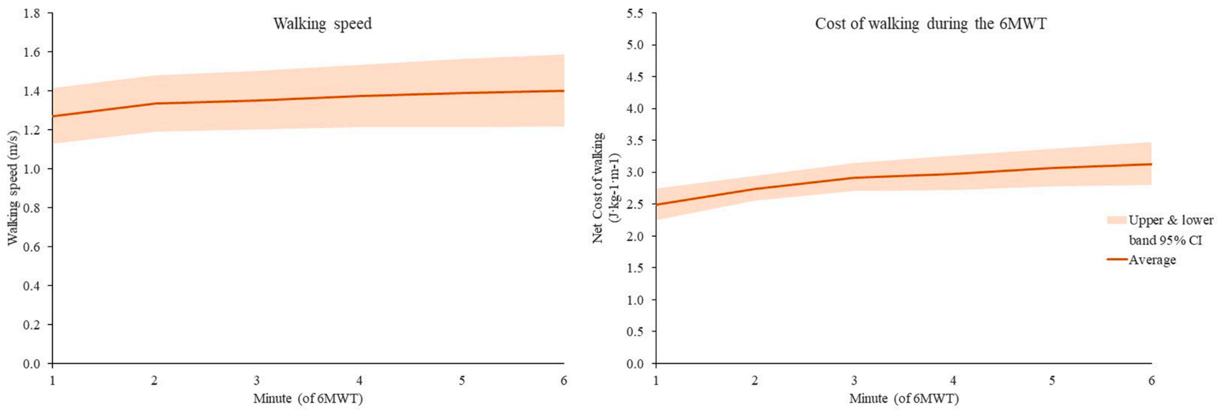

Fig. 1. Left= Walking speed per minute during the six minute walking test (6MWT), Right= Cost of walking (Cw). The shaded area represents the 95% confidence interval (CI). Note that only steady state net Cw of minute 3,4,5,6 are included in the analysis.

Table 2
Gait parameters of interest.

a. Average ± sd per minute	1	2	3	4	5	6
Cost of walking ($J{\bullet}kg^{-1}{\bullet}m^{-1}$)	/	/	2.94 ± 0.49	2.96 ± 0.59	3.07 ± 0.66	3.14 ± 0.73
Walking speed (m/s)*	1.33 ± 0.34	1.39 ± 0.34	1.39 ± 0.36	1.42 ± 0.38	1.43 ± 0.40	1.44 ± 0.42
Cadence (steps/min)	123 ± 11	124 ± 10	124 ± 11	125 ± 11	126 ± 12	126 ± 12
Step length (m)	0.65 ± 0.13	0.67 ± 0.13	0.66 ± 0.14	0.67 ± 0.15	0.67 ± 0.16	0.68 ± 0.17
Step width (m)	0.20 ± 0.06	0.19 ± 0.06	0.20 ± 0.06	0.19 ± 0.06	0.19 ± 0.06	0.19 ± 0.06
b. Variability per minute	**1**	**2**	**3**	**4**	**5**	**6**
Walking speed (%)	6 ± 4	4 ± 3	4 ± 2	5 ± 4	4 ± 2	5 ± 4
Cadence (%)	4 ± 2	3 ± 2	3 ± 2	3 ± 2	3 ± 2	3 ± 2
Step length (%)	4 ± 2	4 ± 2	4 ± 2	4 ± 2	4 ± 3	4 ± 3
Step width (%)	13 ± 7	12 ± 8	12 ± 6	13 ± 6	13 ± 6	14 ± 7
c. Muscle activity per minute	**1**	**2**	**3**	**4**	**5**	**6**
Root Median Square(RMdS)						
Gastrocnemius Medius*	0.14 ± 0.07	0.14 ± 0.08	0.14 ± 0.08	0.15 ± 0.08	0.15 ± 0.08	0.15 ± 0.08
Soleus	0.16 ± 0.05	0.16 ± 0.06	0.16 ± 0.05	0.17 ± 0.05	0.17 ± 0.05	0.18 ± 0.05
Tibialis Anterior*	0.19 ± 0.05	0.20 ± 0.05	0.19 ± 0.05	0.20 ± 0.05	0.21 ± 0.05	0.20 ± 0.05
Median Frequency (MF)						
Gastrocnemius Medius	75 ± 24	77 ± 27	74 ± 25	74 ± 27	76 ± 30	76 ± 30
Soleus*	78 ± 28	76 ± 28	71 ± 29	70 ± 28	69 ± 28	69 ± 29
Tibialis Anterior	84 ± 17	81 ± 18	82 ± 15	81 ± 16	79 ± 18	78 ± 17

Cost of walking is expressed as $J{\bullet}kg^{-1}{\bullet}m^{-1}$=Joules/kilogram bodyweight/distance walked in meters. m/s= meters per seconds. min= minute. m= meter. Variability is expressed as within subject coefficient of variation expressed as percentage ratio of standard deviation to the mean. RMdS= Root Median Square in mV, MF= Median Frequency in Hz.

* An asterisk represents a significant difference between minutes assessed with linear mixed models.

including pwMS. (Hadouiri et al., 2021; Broscheid et al., 2022) This increment is suggested to be clinically significant when compared to other patient populations. (Ries, 2005) Therefore, it can be concluded that the 6MWT induced perceived exertion. However, the increased perceived exertion was not accompanied by changes in objective physical measures of exertion. It was expected that the increase in walking speed was accompanied by either an increase or decrease in Cw, referring to the U-shaped relationship between Cw and walking speed. However, the difference of 7% in Cw between minutes 3 and 6 is slightly beyond the measurement error of 5% and did not change significantly. (Schoffelen and Plasqui, 2018)

Walking speed showed a small increase over time and was not accompanied by changes in other gait parameters of step length, cadence and step width. In contrast to previous literature referring to walking fatigability when decreasing walking speed over the course of the 6MWT, the subjects in our study increased walking speed. These findings are in line with previous studies describing that a decrease in walking speed is not adequate for describing walking fatigability in mildly disabled pwMS (EDSS 0–3.5). (Broscheid et al., 2022; Escudero-Uribe et al., 2019) Although increased gait variability is related to gait deterioration and self-reported fatigue in pwMS with mild disability, (Shema-Shiratzky et al., 2019; Zanotto et al., 2022) the increased RPE in our study was not accompanied by an increased gait variability. This is in line with the results from Crenshaw et al. reporting no change in kinetic and kinematic variability before and after fatigue assessed with an increase in RPE. (Crenshaw et al., 2006) In addition, the positive relationship between gait variability and Cw as described in healthy persons, supports our findings indicating no changes in both variability and Cw over time. (Rock et al., 2018) Although Sebastiao et al. (Sebastião et al., 2018) reported a correlation between gait variability and Cw in pwMS, both outcome measures were not measured simultaneously and even reported a difference in walking speed between both conditions. (Crenshaw et al., 2006; Rock et al., 2018) These findings indicate that the increased RPE - as an indicator for perceived exertion, is not accompanied by an increased variability - as an indicator for physical exertion.

Finally, muscle activation parameters showed significant increases in RMdS of the GM and TA and a decrease in MF of the SOL, indicating no conclusive muscle fatigue. In contrast to previous literature, the increased RPE was not accompanied by muscle fatigue. (Steens et al., 2012) The increased RMdS of the GM and TA could be explained by increased motor unit activation for constant force production due to less force production as the muscle fatigues. In our analysis, walking speed was found to have a main effect and could be an explanatory factor. The increase in RMdS of the GM is in line with previous research assessing muscle fatigue in pwMS. (Eken et al., 2020) The decrease in MF of the SOL could be attributed to a shift towards slower muscle fiber types due to fatigue of fast fiber types and to decreases in conduction velocity. However, our study did not measure lactate levels which could be responsible for a shift in the slower MF spectrum. (Cifrek et al., 2009)

Recent literature indicated that the test-retest reliability of RPE in pwMS following the 6MWT is at most fair (Hadouiri et al., 2021) and suggested the use of objective measurement outcome for fatigue on

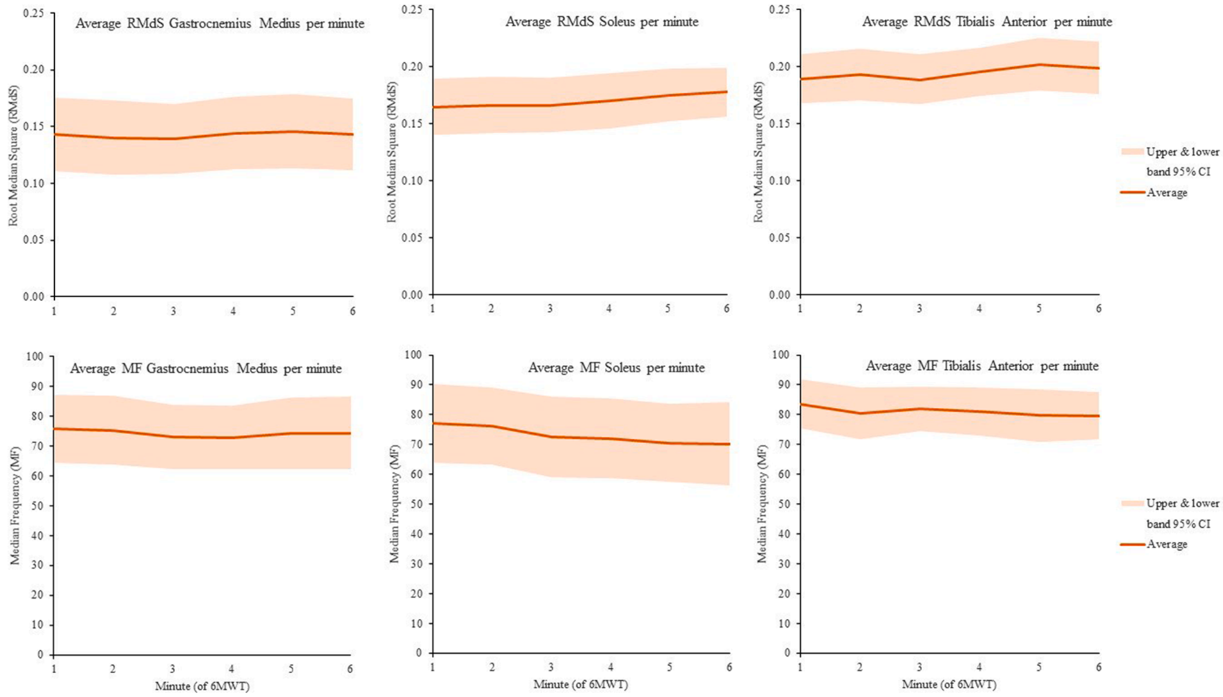

Fig. 2. Muscle activity expressed as Root Median Square (RMdS) in mV and Median Frequency (MF) in Hz averaged per minute for per muscle. The shaded area's represent the 95% Confidence Interval (CI).

exertion. Our attempt to describe more physical measures for fatigue with the absence of changes in the Cw could partly be explained by the delays in metabolic response during changing walking speeds. Aside from a delay caused by the oxygen exchange between the lungs and blood, the consumed oxygen measured from respiratory gasses is used to replace the stored energy which is used for instantaneous force generation. As suggested by Selinger and Donelan, (Selinger and Donelan, 2014) the instantaneous metabolic cost shows a delay of two minutes. It could be suggested that the 6MWT is not an optimal test for assessing changes in Cw due to the variability in walking speed. In comparison to a study by Visch et al., (Visch et al., 2022) our subjects walked with a slightly higher Cw. However, the corresponding walking speed in our study was higher. In contrast, another study reported a higher Cw compared to our results in which, among pwMS, also persons with other neurological disabilities were included. Aside from the differences between the above mentioned studies, both reported a lower Cw with increasing walking speeds. In support of the U-shaped relationship between Cw and walking speed, the decreasing Cw indicates that the subjects did not walk at their energetically optimal speed. Accepting previous evidence on the energetically optimal speed, it can be suggested that the subjects in our study also walked below their energetically optimal speed. (Theunissen et al., 2021) While walking speed increased during the 6MWT, the Cw was expected to decrease. It should however be noted that the individual Cw curves are not the scope of this study and that our subjects were asked to walk at a maximal speed. Finally, decreases in MF of the SOL could be a plausible indication for muscle fatigue since pwMS are known to show decreased ankle plantarflexion. (Almuklass et al., 2018; Wagner et al., 2014) In addition the SOL is primarily responsible for plantarflexion which could explain the absence of decreased MF of the GM since this muscle also induces ankle plantarflexion and knee flexion. (Lenhart et al., 2014) Although the changes in muscle activation are in line with previous literature, there was only an indication for muscle fatigue found. The lack of muscle fatigue could be explained due to the heterogeneity of muscle activation, not leading to an accompanied increase in RMdS and a decrease in MF. However, with muscle activation as the primary source for metabolic energy demand, this might provide the most objective instantaneous indication for physical exertion.

5. Conclusion

The observed increased RPE and walking speed without changes in Cw, indicates that the perceived exertion was not accompanied by an increased physical exertion. Changes in muscle activation of the SOL muscle indicates muscle fatigue we are cautious for definite conclusions. Although the 6MWT reflects daily life walking challenges for pwMS, this test did not show the expected changes in gait parameters in our population. This could be attributed to the mild disease severity of our population. Including a more disabled population or elongated walking protocols could provide a better insight into changes in keeping in mind the daily life walking behavior of pwMS. Future research including the energetically optimal and comfortable walking speed might improve understanding of changing gait parameters related to perceived or physical exertion.

Funding

This work was supported by special research fund 2017 call for doctoral grants in the framework of BOF UHasselt – Maastricht UMC+ cooperation

CRediT authorship contribution statement

Kyra Theunissen: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – original draft. **Guy Plasqui:** Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. **Annelies Boonen:** Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. **Annick Timmermans:** Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. **Pieter Meyns:** Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. **Peter Feys:** Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. **Kenneth Meijer:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors gratefully acknowledge the technical support of Paul Willems and Hans Essers while processing the data. Additionally we would like to thank Raymond Hupperts for the help of the recruitment of participants. Finally, we would like to thank all participants for participating in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104479.

References

Almuklass, A.M., Davis, L., Hamilton, L.D., Vieira, T.M., Botter, A., Enoka, R.M., 2018. Motor unit discharge characteristics and walking performance of individuals with multiple sclerosis. J. Neurophysiol. 119 (4), 1273–1282. https://doi.org/10.1152/jn.00598.2017. Available from:

Arpan, I., Fino, P.C., Fling, B.W., Horak, F., 2020. Local dynamic stability during long-fatiguing walks in people with multiple sclerosis. Gait Posture 76, 122–127. Feb. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0966636219301766.

ATS Statement. Am. J. Respir. Crit. Care Med.. 2002;166(1):111–7. Available from: 10.1164/ajrccm.166.1.at1102.

Borg, G., 1970. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 2 (2), 92–98.

Broscheid, K.C., Behrens, M., Bilgin-Egner, P., Peters, A., Dettmers, C., Jöbges, M., et al., 2022. Instrumented assessment of motor performance fatigability during the 6-min walk test in mildly affected people with multiple sclerosis. Front Neurol. 13, 802516 https://doi.org/10.3389/fneur.2022.802516/full. May 9Available from:

Cifrek, M., Medved, V., Tonković, S., Ostojić, S., 2009. Surface EMG based muscle fatigue evaluation in biomechanics. Clinical Biomechanics 24 (4), 327–340. MayAvailable from: https://linkinghub.elsevier.com/retrieve/pii/S0268003309000254.

Comber, L., Galvin, R., Coote, S., 2017. Gait deficits in people with multiple sclerosis: a systematic review and meta-analysis. Gait Posture 51, 25–35. https://doi.org/10.1016/j.gaitpost.2016.09.026. Available from:

Crenshaw, S.J., Royer, T.D., Richards, J.G., Hudson, D.J., 2006. Gait variability in people with multiple sclerosis. Mult. Scler. 12 (5), 613–619. Oct.

Dalgas, U., Langeskov-Christensen, M., Stenager, E., Riemenschneider, M., Hvid, L.G., 2019. Exercise as medicine in multiple sclerosis-time for a paradigm shift: preventive, symptomatic, and disease-modifying aspects and perspectives. Curr Neurol Neurosci Rep 19 (11), 88. Nov 13.

De Luca, C.J., 1984. Myoelectrical manifestations of localized muscular fatigue in humans. Crit Rev Biomed Eng 11 (4), 251–279.

Donelan, J.M., Kram, R., Kuo, A.D., 2001. Mechanical and metabolic determinants of the preferred step width in human walking. Proc Biol Sci 268 (1480), 1985–1992. Oct 7.

Donelan, J.M., Kram, R., Kuo, A.D., 2002. Mechanical work for step-to-step transitions is a major determinant of the metabolic cost of human walking. J Exp Biol 205 (Pt 23), 3717–3727. Dec.

Eken, M.M., Richards, R., Beckerman, H., Van Der Krogt, M., Gerrits, K., Rietberg, M., et al., 2020. Quantifying muscle fatigue during walking in people with multiple sclerosis. Clinical Biomechanics 72, 94–101. https://doi.org/10.1016/j.clinbiomech.2019.11.020. Available from:

Escudero-Uribe, S., Hochsprung, A., Izquierdo-Ayuso, G., 2019. Gait pattern changes after six-minute walk test in persons with multiple sclerosis. Physiother Res Int 24 (1), e1741. Jan.

Flachenecker, P., Kumpfel, T., Kallmann, B., Gottschalk, M., Grauer, O., Rieckmann, P., et al., 2002. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Mult. Scler. 8 (6), 523–526. Dec.

Goldman, M.D., Marrie, R.A., Cohen, J.A., 2008. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Mult Scler 14 (3), 383–390. https://doi.org/10.1177/1352458507082607. Apr. Available from:

Goldman, M.D., Ward, M.D., Motl, R.W., Jones, D.E., Pula, J.H., Cadavid, D., 2017. Identification and validation of clinically meaningful benchmarks in the 12-item Multiple Sclerosis Walking Scale. Mult Scler 23 (10), 1405–1414. https://doi.org/10.1177/1352458516680749. SepAvailable from:

Hadouiri, N., Monnet, E., Gouelle, A., Decavel, P., Sagawa, Y., 2021. Evaluation of prolonged walking in persons with multiple sclerosis: reliability of the spatio-temporal walking variables during the 6-minute walk test. Sensors 21 (9), 3075. Apr 28Available from: https://www.mdpi.com/1424-8220/21/9/3075.

Heesen, C., Haase, R., Melzig, S., Poettgen, J., Berghoff, M., Paul, F., et al., 2018. Perceptions on the value of bodily functions in multiple sclerosis. Acta Neurol Scand 137 (3), 356–362. Available from: https://pubmed.ncbi.nlm.nih.gov/29205262.

Kalron, A., 2015. Association between perceived fatigue and gait parameters measured by an instrumented treadmill in people with multiple sclerosis: a cross-sectional study. J NeuroEngineering Rehabil 12 (1). Available from: http://www.jneuroengrehab.com/content/12/1/34.

Kempen, J.C., Doorenbosch, C.A., Knol, D.L., de Groot, V., Beckerman, H., 2016. Newly identified gait patterns in patients with multiple sclerosis may be related to push-off quality. Phys Ther 96 (11), 1744–1752. Nov.

Lenhart, R.L., Francis, C.A., Lenz, A.L., Thelen, D.G., 2014. Empirical evaluation of gastrocnemius and soleus function during walking. J Biomech 47 (12), 2969–2974. SepAvailable from: https://linkinghub.elsevier.com/retrieve/pii/S0021929014003881.

Leone, C., Severijns, D., Dolezalova, V., Baert, I., Dalgas, U., Romberg, A., et al., 2016. Prevalence of walking-related motor fatigue in persons with multiple sclerosis: decline in walking distance induced by the 6-minute walk test. Neurorehabil Neural Repair 30 (4), 373–383. May.

Ng, A.V., Miller, R.G., Gelinas, D., Kent-Braun, J.A., 2004. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. Muscle Nerve 29 (6), 843–852. https://doi.org/10.1002/mus.20038. JunAvailable from:

Ries, A.L., 2005. Minimally clinically important difference for the ucsd shortness of breath questionnaire, borg scale, and visual analog scale. COPD: Journal of Chronic Obstructive Pulmonary Disease 2 (1), 105–110. https://doi.org/10.1081/COPD-200050655. JanAvailable from:

Rock, C.G., Marmelat, V., Yentes, J.M., Siu, K.C., Takahashi, K.Z., 2018. Interaction between step-to-step variability and metabolic cost of transport during human walking. Journal of Experimental Biology, jeb.181834. https://doi.org/10.1242/jeb.181834/259680/Interaction-between-step-to-step-variability-and. Jan 1Available from:

Rudroff, T., Kindred, J.H., Koo, P.J., Karki, R., Hebert, J.R., 2014. Asymmetric glucose uptake in leg muscles of patients with Multiple Sclerosis during walking detected by [F-18]-FDG PET/CT. Vol. 35. NeuroRehabilitation 813–823. Nieuwe Hemweg 6b, 1013 Bg Amsterdam, Netherlands: Ios Press.

Savci, S., Inal-Ince, D., Arikan, H., Guclu-Gunduz, A., Cetisli-Korkmaz, N., Armutlu, K., et al., 2005. Six-minute walk distance as a measure of functional exercise capacity in multiple sclerosis. Disabil Rehabil 27 (22), 1365–1371. Nov 30.

Schoffelen, P.F.M., Plasqui, G., 2018. Classical experiments in whole-body metabolism: open-circuit respirometry—Diluted flow chamber, hood, or facemask systems. Eur J Appl Physiol 118 (1), 33–49. https://doi.org/10.1007/s00421-017-3735-5. JanAvailable from:

Sebastião, E., Bollaert, R.E., Hubbard, E.A., Motl, R.W., 2018. Gait variability and energy cost of overground walking in persons with multiple sclerosis: a cross-sectional study. Am J Phys Med Rehabil 97 (9), 646–650. Sep.

Selinger, J.C., Donelan, J.M., 2014. Estimating instantaneous energetic cost during non-steady-state gait. J Appl Physiol 117 (11), 1406–1415. https://doi.org/10.1152/japplphysiol.00445.2014. Dec 1Available from:

Shema-Shiratzky, S., Gazit, E., Sun, R., Regev, K., Karni, A., Sosnoff, J.J., et al., 2019. Deterioration of specific aspects of gait during the instrumented 6-min walk test among people with multiple sclerosis. J Neurol 266 (12), 3022–3030. https://doi.org/10.1007/s00415-019-09500-z. DecAvailable from:

Sloot, L.H., van der Krogt, M.M., Harlaar, J., 2014. Self-paced versus fixed speed treadmill walking. Gait Posture 39 (1), 478–484. JanAvailable from: https://linkinghub.elsevier.com/retrieve/pii/S0966636213005808.

Steens, A., de Vries, A., Hemmen, J., Heersema, T., Heerings, M., Maurits, N., et al., 2012. Fatigue perceived by multiple sclerosis patients is associated with muscle fatigue. Neurorehabil Neural Repair 26 (1), 48–57. https://doi.org/10.1177/1545968311416991. JanAvailable from:

Stella, A.B., Morelli, M.E., Giudici, F., Sartori, A., Manganotti, P., di Prampero, P.E., 2020. Comfortable walking speed and energy cost of locomotion in patients with multiple sclerosis. Vol. 120. Eur. J. Appl. Physiol. 551–566. One New York Plaza, Suite 4600, New York, Ny, United States: Springer.

Theunissen, K., Plasqui, G., Boonen, A., Brauwers, B., Timmermans, A., Meyns, P., et al., 2021. The relationship between walking speed and the energetic cost of walking in persons with multiple sclerosis and healthy controls: a systematic review. Neurorehabil Neural Repair 35 (6), 486–500. https://doi.org/10.1177/15459683211005028. Jun. Available from:

van den Bogert, A.J., Geijtenbeek, T., Even-Zohar, O., Steenbrink, F., Hardin, E.C., 2013. A real-time system for biomechanical analysis of human movement and muscle function. Med Biol Eng Comput 51 (10), 1069–1077. https://doi.org/10.1007/s11517-013-1076-z. OctAvailable from:

van der Krogt, M.M., Delp, S.L., Schwartz, M.H., 2012. How robust is human gait to muscle weakness? Gait Posture 36 (1), 113–119. MayAvailable from: https://linkinghub.elsevier.com/retrieve/pii/S0966636212000392.

Van Geel, F., Veldkamp, R., Severijns, D., Dalgas, U., Feys, P., 2020. Day-to-day reliability, agreement and discriminative validity of measuring walking-related performance fatigability in persons with multiple sclerosis. Mult Scler 26 (13), 1785–1789. https://doi.org/10.1177/1352458519872465. Nov. Available from:

Van Marken Lichtenbelt, W.D., Westerterp, K.R., Wouters, L., 1994. Deuterium dilution as a method for determining total body water: effect of test protocol and sampling time. Br J Nutr 72 (4), 491–497. OctAvailable from: https://www.cambridge.org/core/product/identifier/S0007114594001546/type/journal_article.

Visch, L., Oudenhoven, L.M., Timmermans, S.T., Beckerman, H., Rietberg, M.B., de Groot, V., et al., 2022. The relationship between energy cost of walking, ankle push-off and walking speed in persons with multiple sclerosis. Gait Posture 98, 160–166.

OctAvailable from: https://linkinghub.elsevier.com/retrieve/pii/S0966636222004805.
Wagner, J.M., Kremer, T.R., Van Dillen, L.R., Naismith, R.T., 2014. Plantarflexor weakness negatively impacts walking in persons with multiple sclerosis more than plantarflexor spasticity. Arch Phys Med Rehabil 95 (7), 1358–1365. JulAvailable from: https://linkinghub.elsevier.com/retrieve/pii/S0003999314001373.
Westerterp, K.R., Wouters, L., van Marken Lichtenbelt, W.D., 1995. The maastricht protocol for the measurement of body composition and energy expenditure with labeled water. Obes. Res. 3, 49–57. https://doi.org/10.1002/j.1550-8528.1995.tb00007.x. MarAvailable from:
Zanotto, T., Sosnoff, J.J., Ofori, E., Golan, D., Zarif, M., Bumstead, B., et al., 2022. Variability of objective gait measures across the expanded disability status scale in people living with multiple sclerosis: a cross-sectional retrospective analysis. Mult Scler Relat Disord 59, 103645. MarAvailable from: https://linkinghub.elsevier.com/retrieve/pii/S2211034822001602.
Zeni, J.A., Richards, J.G., Higginson, J.S., 2008. Two simple methods for determining gait events during treadmill and overground walking using kinematic data. Gait Posture 27 (4), 710–714. MayAvailable from: https://linkinghub.elsevier.com/retrieve/pii/S0966636207001804.