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ORIGINAL REPORT

AEROBIC INTENSITY AND PACING PATTERN DURING THE SIX-MINUTE WALK TEST IN PATIENTS WITH MULTIPLE SCLEROSIS

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Objective: **To examine the aerobic intensity level and pacing pattern during the 6-min walk test (6MWT) in persons with multiple sclerosis, taking into account time of day, fatigue, disability level and multiple sclerosis subtype.**
Design: **Cross-sectional study.**
Subjects/patients: **Eighty multiple sclerosis patients (Expanded Disability Status Scale, EDSS ≤6.5).**
Methods: **Participants performed the 6MWT at 3 different time-points (morning, noon, afternoon) during 1 day. Heart rate and pacing pattern (distance covered every minute) were registered. A sub-group analysis determined the effects of fatigue, disability level and multiple sclerosis subtype.**
Results: **The relative aerobic intensity was constant throughout the day (67±10% of estimated maximal heart rate). In all sub-groups heart rate increased and distance walked declined after the first minute ($p<0.001$). The mild EDSS sub-group showed a slightly larger increase throughout the 6MWT in heart rate development, while no differences were seen in sub-groups of fatigue and multiple sclerosis subtype. In most sub-groups walking speed was fastest in the first minute and constant during the final 4 minutes.**
Conclusion: **In patients with multiple sclerosis aerobic intensity is moderate during the 6MWT and unaffected by time of day. Disability may have some influence on aerobic intensity, but not on pacing strategy during the 6MWT, whereas neither fatigue nor multiple sclerosis subtype has any effect.**

Key words: heart rate; walking capacity; walking performance; 6MWT.

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INTRODUCTION

Walking capacity is perceived as one of the most valuable bodily functions among persons with multiple sclerosis (MS) (1–3), but walking capacity is often impaired in these patients (4–7). Consequently, walking capacity tests are frequently applied in routine practice and intervention trials. Tests of walking capacity can be categorized into short (e.g. the timed 25-foot walk) and long (e.g. the 6-min walk test; 6MWT) tests, which are thought to evaluate maximal walking speed and walking endurance, respectively. The 6MWT (8) is considered the "gold standard" when measuring walking endurance across a variety of patient groups (9). Despite its wide use also in neurological patients (10), it is not known whether the cardiorespiratory system is stressed when the 6MWT is performed in these patients, who are characterized by both motor deficits and occurrence of fatigue. To evaluate this, one can examine aerobic intensity in terms of the (relative) oxygen consumption and/or (relative) heart rate (HR). Measurement of oxygen consumption is difficult to perform accurate during a field test, whereas HR is easily measured. Expressing aerobic intensity in relative terms (i.e. as a percentage of the maximal HR) is of importance, since HR is age-dependent (11) and, therefore, may differ when patients are divided into subgroups based on increasing disability level.

Savci et al. (6) reported a moderate relative intensity (69% of HR_{max}) in 30 mild to severely impaired MS patients (EDSS < 6.5) during the 6MWT (6). However, no disability subgroups were compared and HR measurements were performed only before and after the 6MWT. A recent publication by Bosnak-Guclu et al. (12) showed that HR measured immediately after the 6MWT was higher in mild (EDSS: 0–2; 137 bpm) compared with moderate (EDSS: 2.5–4.5; 116 bpm) MS patients, but the study did not report the relative aerobic intensity (taking into account the age differences between the 2 groups) and did not include patients with an EDSS > 4.5. To our knowledge, no studies have evaluated the relative aerobic intensity in a large group of MS patients with a wide range of disabilities during the 6MWT.

In a previous publication from the present study it was shown that the 6MWT performance remains unchanged throughout the day, although patients report an increase in fatigue at noon and in the afternoon compared with in the morning (13). It is, however, unclear whether the aerobic intensity is affected by time of day, as perceived fatigue may be related to the aerobic intensity during physical performance, such as during the 6MWT. Furthermore, the level of disability can affect the economy of walking during the 6MWT (14), but it has not been established how the level of disability affects the relative aerobic intensity.

Another aspect of the 6MWT is the applied pacing pattern, which is typically defined as the distance covered every minute of the test. A study in 40 mild to moderately impaired MS patients reported that the walking speed during the first 2 minutes of the 6MWT was significantly faster than during the last 4 minutes, where walking speed was constant (15). Based on 40 MS patients, Goldman et al. (16) concluded that the pacing pattern was related to the disability level of the participants, since mildly impaired patients increased speed at the end of the test, whereas moderately and severely impaired patients stabilized or continuously slowed down throughout the test. However, only 6 participants were categorized as severely disabled, necessitating confirmation of this finding in larger samples. Pacing pattern was also investigated in MS patients with different disability levels by Phan-Ba et al. (17), who observed that patients with marked pyramidal, cerebellar or sensitive dysfunction in particular (Kurtzke functional system scores > 2) show a slowing of speed during the performance of a 500-m walking test. Recently, we published a multicentre study on different walking capacity tests in patients with MS (9, 13). Part of these data has now been further analysed to examine: (*i*) the aerobic intensity level and the pacing pattern during the 6MWT in MS patients, and (*ii*) if aerobic intensity and pacing pattern are influenced by fatigue, disability and MS subtype. We hypothesized that the relative aerobic intensity would be moderate overall, and that walking speed would be highest during the first part of the 6MWT and then increase, stabilize or reduce in the final minute(s), depending on the disability level (mild, moderate or severe, respectively) of the patient.

METHODS

The present data were collected during a multi-centre study performed within the RIMS network (a European Network for best Practice and Research in MS Rehabilitation; www.eurims.org). Detailed descriptions of the methodology and study design have been reported elsewhere and are summarized below (9, 13).

Setting, subjects and clinical characteristics

Included patients had a diagnosis of MS according to the McDonald criteria (18), and an EDSS (19) ≤ 6.5, indicating ability to walk at least 20 m independently with or without assistive device. Patients with a relapse in the last month prior to the study, or relapse-related treatment with glucocorticoids were excluded, as were patients with an orthopaedic, cardiovascular or other neurological conditions interfering with walking. Participants joined the study after written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the Human Ethics Committee of the leading University of Hasselt as well as by the local ethics committees of participating centres.

The multicentre study (20) included 102 participants, but not all centres were able to provide HR data. Moreover, 6 European centres additionally provided HR data for this part of the study. A convenience sample of 80 MS patients was assembled from out-patient ($n=2$) and in-patient ($n=4$) centres. To standardize data collection, a comprehensive booklet describing procedures and test instructions in detail were distributed to each involved site and a tutorial was given. Descriptive clinical characteristics are presented in Table I, including disability level (EDSS), type of MS and overall fatigue level measured by the Modified Fatigue Impact Scale (MFIS) (21).

Experimental design, procedure and outcome measures

Effects of time of day on the 6MWT were investigated by means of repeated measurements at 3 standardized time-points, i.e. 09.00–10.00 h, 12.00–13.00 h, and 15.00–16.00 h. A shift of 1 h was allowed, to adapt to the local routine schedule in participating centres, as long as a 3-h interval between measurements was maintained.

Aerobic intensity and pacing pattern during the 6-min walk test

The main experimental outcomes of this study were: (*i*) aerobic intensity expressed in absolute beats/minute (bpm) and as a percentage of age-predicted maximal heart rate (HR_{max}), and (*ii*) pacing pattern quantified as distance covered at each minute of the 6MWT. Data on both HR and distance covered was registered every minute during the 6MWT (see below).

In accordance with the protocol of Goldman et al. (16), participants walked up and down a 30-m trajectory, and were instructed to cover as much distance as possible during 6 min. The use of assistive devices was permitted, while patients were not verbally encouraged, in order to avoid any bias potentially induced by assessors from different centres. On the 30-m trajectory markings were placed every 1 m, allowing the assessor to register the distance walked every minute.

The 12-Item MS Walking Scale – 12 (MSWS-12) was used as a patient-based measure of the impact of MS on walking and was completed before the walking tests. The transformed MSWS-12 score is presented (22).

Heart rate

HR was monitored using POLAR heart rate monitors (Polar Electro, Oulu, Finland). The POLAR belt was attached to the chest of the participant, while the POLAR watch was worn by the observer while walking slightly behind the participant for a limited distance every minute. This was done: (*i*) to accurately note the distance in metres covered every minute during the 6MWT; and (*ii*) to capture and note the patient's HR every minute without disturbing the attention and performance of the patient. Resting HR was measured while the participants were resting in a chair and was determined as the lowest steady state HR registered within a 2-min time-frame.

Data processing

Data were stratified according to time of day, EDSS, fatigue, MS subtype (relapsing-remitting (RR), secondary progressive (SP), or primary progressive (PP)).

Neurological impairment. Identical to Goldman et al. (16), people with MS were allocated into subgroups with mild (EDSS: 1–2.5; $n=14$), moderate (EDSS: 3–4, $n=32$) and severe (EDSS: 4.5–6.5; $n=34$) neurological impairment.

Fatigue. A $MFIS_{total}$ score of 38 served as cut-off when differentiating between fatigued and non-fatigued MS patients (23). A further subgroup analysis based on the $MFIS_{physical}$ subscore was also performed applying a cut-off score of 15 (data not shown).

Normalization of the 6MWT. The 6MWT was normalized to published norm-data by applying the regression equations determined by Enright et al. (23).

Age-predicted HR_{max}. Age-predicted HR_{max} values during the 6MWT were calculated based on the equations provided by Fairbarn et al. (24)

Change in HR. The change in HR during the 6MWT was calculated as: mean HR during the 6MWT minus resting HR.

Statistical analysis

Descriptive statistics were calculated for the total group. To examine baseline differences between the subgroups (based on EDSS, Fatigue and MS subtype), Student's t-tests and one-way analysis of variance

(ANOVA) were applied for parametric variables (EDSS, age, MFIS), while for non-parametric variables (gender, MS subtype), differences between subgroups were analysed with a χ^2 test.

To examine the influence of time of day on absolute and relative HR during the 6MWT, a one-way ANOVA was performed. Since time of day influenced neither HR nor distance, mean data from morning, noon and afternoon were used in further analyses.

Student's *t*-test was used to analyse differences in mean distance covered during the 6MWT and resting and mean (relative) HR between the fatigue subgroups, while a one-way ANOVA was used to detect differences between the EDSS subgroups and MS subtypes.

A 2-way (subgroup × min) ANOVA for repeated measurements was used to detect differences in aerobic intensity and pacing pattern. Tukey *post-hoc* tests were applied for contrast analyses when a subgroup × min interaction was present.

A Pearson product correlation test was used to examine associations between the 6MWT distance, mean relative HR, MFIS, MSWS-12 and EDSS. Analyses were performed using Stata version 11 (StataCorp LP, Texas, USA) and SigmaPlot 11 (Systat Software Inc., Illonois, USA) with level of significance set at $p < 0.05$.

RESULTS

Tables I and II show clinical characteristics and experimental outcome measures for the whole sample and sub-groups, respectively. The different MS subtypes differed significantly with respect to age, EDSS and gender distribution (Table II).

Aerobic intensity

As depicted in Table III, neither resting nor mean absolute and relative HR during the 6MWT differed significantly throughout the day. The mean relative intensity across time of day was 67 ± 10% of the age-predicted HR_{max}. Resting HR did not differ between any subgroups (Table IV), although a trend was found in relative HR for the EDSS sub-groups ($p = 0.06$). The mean absolute HR during the 6MWT significantly differed between the sub-groups of EDSS (Mild > Moderate = Severe) and MS subtype (RR > PP), while a difference in HR between the fatigue subgroups based on $MFIS_{total}$ score approached significance ($p = 0.06$). Similar results were found when dividing groups based on the $MFIS_{physical}$ subscore (data not shown). When comparing the mean relative HR, a tendency ($p = 0.07$) towards a difference between the EDSS subgroups was observed (Fig. 1). The min × group interaction was significant for both the absolute and relative HR for the EDSS subgroups (for details on post-hoc tests see Fig. 1). No time × group effect on neither absolute or relative HR were seen for gender (data not shown).

Pacing pattern

Table V shows that a significant difference in total distance walked during the 6MWT was found between the subgroups of EDSS (mild > moderate > severe), and MS subtype (RR > SP = PP), whereas no difference was observed between the fatigue sub-groups (same result when applying the $MFIS_{physical}$ subscore, data not shown). Furthermore, Table V contains detailed information regarding distance walked during each minute of the 6MWT. No min × group interaction was found for any subgroup (including gender, data not shown), although a trend towards significance ($p = 0.09$) was noted not fully excluding some potential difference

Table I. *Patient characteristics (*n = *80)*

Variables	
Age, years, mean (SD) [range]	50 (9) [26–69]
Height, cm, mean (SD) [range]	170 (9) [153–191]
Weight, kg, mean (SD) [range]	73 (17) [48–119]
Gender, M/F, *n*	32/48
Type of MS, RR/SP/PP, *n*	38/27/15
EDSS, a.u., mean (SD) [range]	4.1 (1.5) [1–6.5]
Time since diagnosis, years, mean (SD) [range]	12 (7) [1–31]
MFIS, a.u., mean (SD) [range]	42 (14) [9–72]
MFIS-physical, mean (SD) [range]	20 (7) [3–35]
MSWS-12 transformed, %, mean (SD) [range]	56 (22) [0–98]
Assistive device, +/–, mean (SD) [range]	31/49

a.u.: arbitrary unit; EDSS: Expanded Disability Status Scale; MFIS: Modified Fatigue Impact Scale; MSWS-12: MS Walking Scale 12.

Table II. *Descriptive characteristics of the patient sample according to subgroup*

	EDSS			
	Mild (*n* = 14)	Moderate (*n* = 32)	Severe (*n* = 34)	*p*-value
Age, years, mean (SD)	47 (7)	50 (9)	52 (10)	0.20[a]
MFIS, a.u., mean (SD)	43 (11)	40 (14)	43 (15)	0.56[a]
Gender, M/F, *n*	3/11	13/19	16/18	0.26[b]
Sub-type, RR/SP/PP, *n*	12/2/0	16/8/8	10/17/7	0.01[b]
	Fatigue			
	Non-fatigued (*n* = 25)		Fatigued (*n* = 55)	*p*-value
Age, years, mean (SD)	49 (9)		51 (9)	0.33[c]
EDSS, a.u., mean (SD)	4.0 (1.5)		4.2 (1.5)	0.37[c]
Gender, M/F, *n*	9/16		23/32	0.62[b]
Sub-type, RR/SP/PP, *n*	15/9/1		23/18/14	0.07[b]
	Sub-type			
	RR (*n* = 38)	SP (*n* = 27)	PP (*n* = 15)	*p*-value
Age , years, mean (SD)	47 (8)	51 (10)	56 (7)	< 0.01[a]
EDSS, a.u., mean (SD)	3.6 (1.5)	4.6 (1.3)	4.7 (1.3)	< 0.01[a]
MFIS, a.u., mean (SD)	39 (15)	42 (14)	47 (8)	0.22[a]
Gender, M/F, *n*	10/28	11/16	11/4	< 0.01[b]

[a]One-way analysis of variance; [b]chi^2-test; [c]*t*-test.
a.u.: arbitrary unit; EDSS: Expanded Disability Status Scale; SD: standard deviation; MFIS: Modified Fatique Impact Scale; M: male; F: female; RR: relapsing remitting; SP: secondary progressive; PP: primary progressive.

Table III. *Effect of time of day on distance and heart rate (HR) during the 6-min walk test (*n = *80)*

	Morning Mean (SD)	Noon Mean (SD)	Afternoon Mean (SD)	*p*-value[a]
% pred. distance, %	64 (28)	65 (30)	65 (30)	0.96
Resting HR, bpm	78 (13)	76 (12)	79 (13)	0.30
% est. HR_{max}	46 (7)	45 (7)	47 (8)	0.31
HR, bpm	112 (16)	112 (18)	114 (18)	0.63
% est. HR_{max}	67 (9)	66 (11)	68 (11)	0.59
Change in HR, bpm	34 (15)	36 (17)	35 (17)	0.81

[a]One-way analysis of variance. % pred distance: percentage walked of predicted distance; est.: estimated; HR_{max}: mean HR expressed as percentage of estimated max HR; SD: standard deviation.

Table IV. *Absolute and relative heart rate during the 6-min walk test in patients with multiple sclerosisww*

		Heart Rate rest		Heart Rate		Minute						*p*-value		
		Mean (SD)	*p*-value	Mean (SD)	*p*-value	1st Mean (SD)	2nd Mean (SD)	3rd Mean (SD)	4th Mean (SD)	5th Mean (SD)	6th Mean (SD)	Minute	Group	Interaction
Heart Rate (bpm)														
Total	All ($n=80$)	78 (12)	–	113 (17)	–	108 (14)	112 (16)	113 (17)	114 (18)	115 (18)	116 (19))	<0.001[b(r)]	–	–
EDSS	Mild ($n=14$)	76 (10)	0.19[b]	124 (16)	0.02[b]	116 (14)	122 (16)	124 (16)	125 (16)	127 (17)	130 (18)	<0.001[c]	0.02[c]	<0.001[c]
	Moderate ($n=32$)	76 (11)		110 (14)		106 (11)	109 (13)	110 (14)	111 (14)	112 (15)	114 (17)			
	Severe ($n=34$)	81 (13)		111 (18)		107 (16)	110 (17)	110 (18)	111 (19)	112 (19)	112 (20			
MFIS	Non-Fatigued ($n=25$)	80 (13)	0.24[a]	118 (17)	0.06[a]	112 (14)	117 (16)	118 (18)	119 (19)	120 (19)	121 (19)	<0.001[c]	0.063[c]	0.721[c]
	Fatigued ($n=55$)	77 (11)		110 (16)		106 (14)	110 (15)	110 (17)	111 (17)	112 (17)	113 (19)			
Sub-type	RR ($n=38$)	77 (11)	0.59[b]	117 (17)	0.01[b]	112 (13)	116 (16)	117 (17)	118 (18)	119 (18)	121 (20)	<0.001[c]	0.015[c]	0.263[c]
	SP ($n=27$)	80 (13)		112 (18)		108 (16)	112 (17)	112 (18)	113 (19)	114 (18)	114 (19)			
	PP ($n=15$)	78 (11)		103 (9)		99 (8)	102 (8)	103 (9)	103 (10)	104 (11)	105 (11)			
Relative Heart Rate (%)														
Total	All ($n=80$)	46 (7)	–	67 (10)	–	64 (8)	67 (9)	67 (10)	67 (10)	68 (11)	69 (11)	<0.001[b(r)]	–	–
EDSS	Mild ($n=14$)	44 (6)	0.06[b]	72 (9)	0.07[b]	68 (8)	71 (9)	73 (9)	73 (9)	74 (10)	76 (10)	<0.001[c]	0.07[c]	<0.001[c]
	Moderate ($n=32$)	45 (7)		65 (8)		63 (7)	65 (8)	65 (8)	66 (9)	66 (9)	68 (10)			
	Severe ($n=34$)	48 (8)		66 (11)		64 (9)	66 (10)	66 (11)	67 (12)	67 (12)	67 (12)			
MFIS	Non-Fatigued ($n=25$)	47 (7)	0.44[a]	69 (10)	0.13[a]	66 (8)	69 (9)	69 (10)	70 (11)	71 (11)	71 (11)	<0.001[c]	0.124[c]	0.779[c]
	Fatigued ($n=55$)	46 (7)		66 (10)		63 (8)	65 (9)	66 (10)	66 (10)	67 (10)	67 (11)			
Sub-type	RR ($n=38$)	45 (6)	0.20[b]	69 (10)	0.15[b]	65 (8)	68 (9)	68 (10)	69 (11)	70 (11)	71 (12)	<0.001[c]	0.143[c]	0.349[c]
	SP ($n=27$)	47 (8)		67 (11)		64 (10)	67 (11)	67 (11)	67 (12)	68 (12)	68 (12)			
	PP ($n=15$)	48 (7)		63 (5)		61 (4)	62 (4)	63 (5)	63 (5)	63 (6)	64 (6)			

[a]*t*-test; [b]One-way ANOVA (repeated measures); [c]Two-way ANOVA for repeated measures. EDSS: Expanded Disability Scale; MFIS: Modified Fatique Impact Scale; RR: relapsing remitting; SP: secondary progressive; PP: primary progressive; SD: standard deviation; ANOVA: analysis of variance.

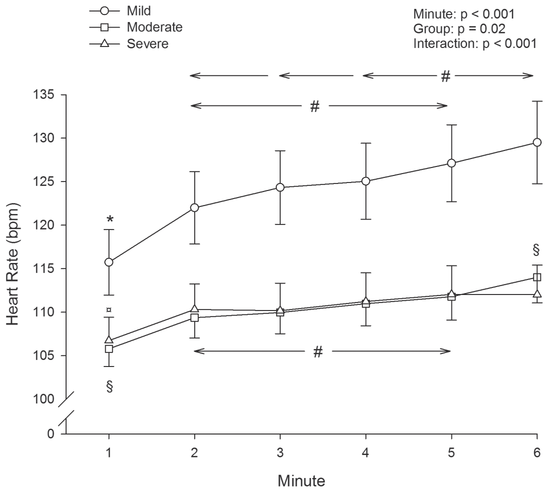

Fig. 1. Heart rate (mean ± standard error) every minute of the 6-min walk test for the different Expanded Disability Status Scale sub-groups (mild, moderate and severe). The result of the 2-way analysis of variance for repeated measures is shown in the upright corner. *, §, and ¤ post-hoc test showing significant difference from all other minutes within-group for mild, moderate and severe subgroups, $p<0.05$. #*post-hoc* test showing significant difference between minutes, $p<0.05$.

between EDSS subgroups. For all subgroups, a significant effect in minutes was found, showing that distance walked declined throughout the test. Patients in the moderate and severe EDSS subgroups walked longest during the first minute compared with all other minutes, and minutes 3–6 were stable for all EDSS subgroups. Group differences in distance covered per minute persisted throughout the test (Fig. 2).

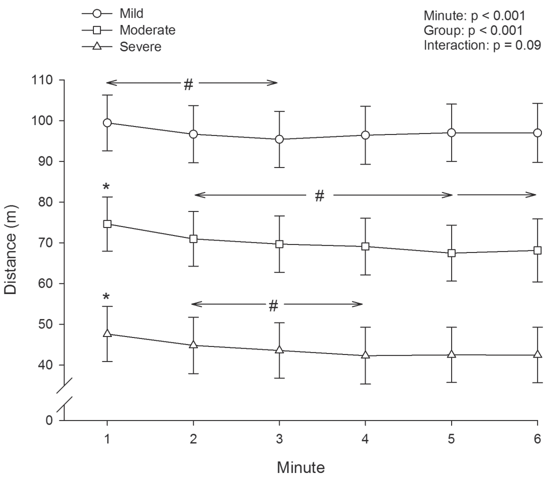

Fig. 2. Distance walked every minute (mean ± 95% confidence interval (CI)) during the 6-min walk test for the different Expanded Disability Status Scale sub-groups (mild, moderate and severe). The result of the 2-way analysis of variance for repeated measures is shown in the upright corner. **Post-hoc* test showing significant difference from all other minutes within group, $p<0.05$. #*Post-hoc* test showing significant difference between minutes, $p<0.05$.

Table V. *Pacing pattern during the 6-min walk test in patients with multiple sclerosis*

		Total		Minute						*p*-value		
		Mean (SD)	*p*-value	1st Mean (SD)	2nd Mean (SD)	3rd Mean (SD)	4th Mean (SD)	5th Mean (SD)	6th Mean (SD)	Minute	Group	Interaction
6MWT Distance (m)												
Total	All (*n*=80)	382 (159)	–	67 (26)	64 (26)	63 (26)	63 (27)	62 (27)	62 (28)	<0.001[b]	–	–
EDSS	Mild (*n*=14)	582 (72)	<0.001[b]	100 (12)	97 (12)	95 (12)	97 (12)	97 (12)	97 (13)	<0.001[c]	<0.001[c]	0.09[c]
	Moderate (*n*=32)	420 (114)		75 (18)	71 (19)	70 (19)	69 (19)	68 (19)	68 (21)			
	Severe (*n*=34)	263 (116)		48 (19)	45 (20)	44 (20)	42 (20)	42 (19)	42 (20)			
MFIS	Non-Fatigued (*n*=25)	389 (154)	0.78[a]	68 (26)	65 (26)	65 (25)	63 (26)	63 (26)	65 (26)	<0.001[c]	0.780[c]	0.164[c]
	Fatigued (*n*=55)	378 (163)		67 (27)	64 (27)	62 (27)	62 (28)	61 (27)	61 (29)			
Sub-type	RR (*n*=38)	437 (163)	0.01[b]	77 (26)	73 (27)	72 (27)	71 (29)	71 (28)	72 (28)	<0.001[c]	0.010[c]	0.436[c]
	SP (*n*=27)	336 (153)		59 (25)	57 (25)	55 (25)	55 (26)	55 (25)	55 (27)			
	PP (*n*=15)	323 (116)		58 (19)	55 (20)	54 (21)	54 (19)	51 (18)	51 (21)			

[a]*t*-test; [b]One-way analysis of variance (repeated measures); [c]Two-way analysis of variance for repeated measures.

Table VI. *Correlations between 6-min walk test (6MWT), aerobic intensity, Expanded Disability Scale (EDSS) and self-reported fatigue and walking ability*

		Mean relative HR	6MWT	MFIS-total	MFIS-physical	MSWS-12-transformed	EDSS
Mean relative HR	Correlation coef.	–	0.245	−0.208	−0.284	−0.418	−0.153
	p-value		0.03	0.06	0.01	<0.001	0.17
6MWT	Correlation coef.	0.245	–	−0.102	−0.283	−0.624	−0.811
	p-value	0.03		0.367	0.01	<0.001	<0.001

HR: Heart rate; MFIS: Modified Fatigue Impact Scale; MSWS-12: Multiple Sclerosis Walking Scale-12.

Correlations

Table VI shows the results of the correlation analyses. A weak significant positive correlation between the distance walked and the mean relative HR during the 6MWT was observed (Fig. 3A). Mean relative HR and 6MWT correlated negatively with $MFIS_{physical}$ and MSWS-12, respectively (Fig. 3B, C), while no significant correlation was found with $MFIS_{total}$. Finally, a strong negative correlation was observed between the 6MWT and the EDSS (Fig. 3D).

DISCUSSION

The present study investigated effects of time of day on aerobic intensity and pacing pattern in subgroups with different disability, fatigue level and type of MS. Aerobic intensity of the 6MWT did not differ throughout the day, was overall moderate, and to a minor extent, influenced by disability level, but not by fatigue or MS subtype. Pacing pattern was not influenced by disability level, fatigue and MS subtype.

Aerobic intensity

To allow direct comparison of aerobic intensity during the 6MWT across studies application of relative HR values would be needed. However, most studies do not provide relative HR values, thus it is nessessary to look at absolute HR values for any comparison, despite these being not directly comparable across studies. Keeping this in mind, the measured aerobic intensity (mean absolute HR ~112 bpm) for all subjects during the 6MWT corresponded well to the values (101–111 bpm) reported in a small Italian study ($n=11$; EDSS: 1–3.5) (4) and a larger Finnish study (112 bpm, $n=120$; EDSS: 0–6.5) (25). However, HR during the 6MWT may depend on severity of ambulatory dysfunction, as a recent publication of Bosnak-Guclu et al. revealed that HR measured immediately after the 6MWT, was higher in mild (EDSS: 0–2; 137 bpm) compared with moderate (EDSS: 2.5–4.5; 116 bpm) MS patients (12). However, the study did not report the relative aerobic intensity taking into account the reported age differences between the 2 groups. The mean absolute HR during the 6MWT in our study was also higher in the mild group compared with both the moderate and the severe group, although the latter 2 groups showed significantly different gait velocity. The lack of difference in aerobic intensity between the moderate and the severe group indicates that the latter group may have reduced walking economy, since the walking distance was markedly lower. It is noted, however, that when HR was expressed relative to the age-predicted HR_{max}, only a trend ($p=0.07$) towards EDSS subgroup differences existed, indicating that the differences in absolute HR may be partly

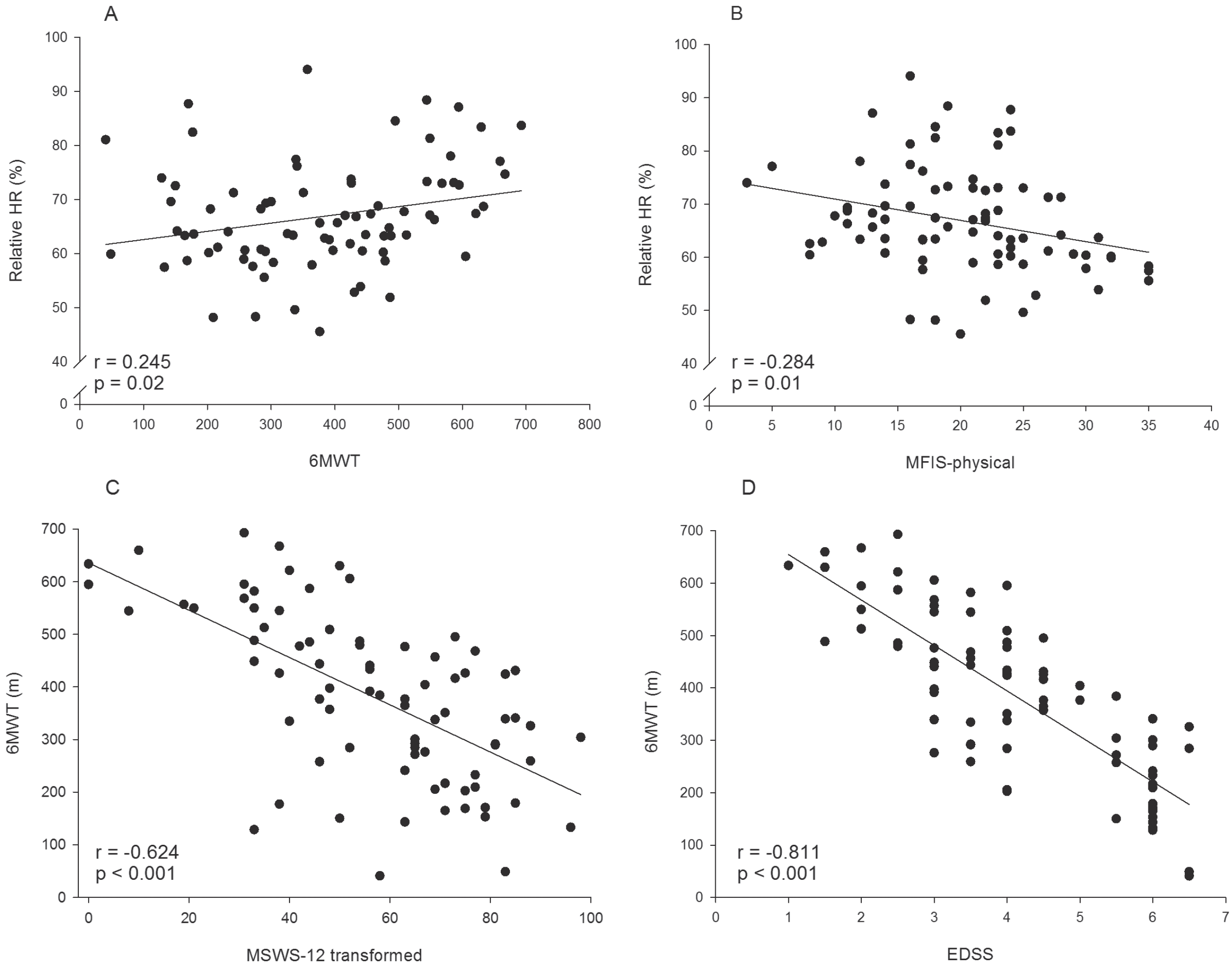

Fig. 3. (A) and (B): Correlations between 6-min walk test (6MWT) and Modified Fatigue Impact Scale $(MFIS)_{physical}$ score and the mean relative heart rate (HR) during the 6MWT, respectively. (C) and (D): Correlations between total distance walked in the 6MWT and MSWS-12 (transformed) and EDSS score, respectively. Correlation coefficient and significance level is shown for each figure.

explained by age differences, or that even larger sample sizes are required to capture small differences caused by disability.

Several studies have reported on the differences between resting HR and HR during or after the 6MWT (highest HR during the 6MWT (12), at the 6th minute (25) or just after the test (6)). In our study the mean change in HR from rest to the 6th minute was 38 bpm, corresponding to the findings of Paltamaa et al. (25) (45 bpm) and Savci et al. (6) (34 bpm). When looking at the EDSS subgroups, Bosnak-Guclu et al. (12) observed that HR increased more in the mild group than in the moderate group (EDSS: 0–2; 54 bpm and EDSS: 2.5–4.5; 30 bpm). This is similar to the present study, which expands previous research by also including patients with severe ambulatory dysfunction (EDSS > 4.5).

The 6MWT is usually regarded as a measure of endurance and cardiorespiratory fitness, on top of what is encompassed by a short walk test (i.e. motor control, strength, balance, adaptations in gait pattern) (16, 26). Savci et al. (6) reported a relative intensity of 69% of age-predicted HR_{max}. Although our estimation of HR_{max} was based on a slightly different calculation, we found a similar (67% of HR_{max}) relative intensity during the 6MWT, indicating that the aerobic intensity during the test is far from maximal effort, also in persons with mild MS, and the intensity level may be labelled moderate only. Consequently, the intensity applied during the 6MWT is not close to the maximal oxygen uptake (VO_2max) which, therefore, will not be expected to be the factor limiting 6MWT performance in MS patients. Moderate correlations between the 6MWT and $VO_{2\text{-peak}}$ have been reported in patients with advanced heart failure ($r = 0.64$) (27), patients after heart transplantation ($r = 0.74$) (28) and, in patients with end-stage lung disease ($r = 0.73$) (29)). In stroke patients, who may be more comparable to MS patients, findings are inconsistent, with correlations ranging from low to strong ($r = 0.37$–0.84) (30–34). Such contradictory findings from other pathologies on the associations between the 6MWT and $VO_{2\text{-peak}}$ emphasize that further studies on the topic are warranted in neurological patients including MS. Also, this indicates that motor impairments in some patients/pathologies may interfere with the normal physiological demands of the 6MWT.

Pacing pattern

The present study showed that walking speed during the first minute differed from the speed during the last 5 min, and that walking speed was constant from minutes 3–6. This is in line with Gijbels et al. (15), who reported, that walking speed during the first 2 min of the 6MWT was significantly faster than during the last 4 min a slower but constant speed was observed. The present study expands on previous studies by confirming this pacing pattern for all subgroups regardless of disability level, fatigue or type of MS. However, it should be noted that we observed a non-significant trend ($p=0.09$) for a time × group interaction for the EDSS subgroups. Also, quite large standard deviations were found in the severely disabled EDSS group, suggesting that quite large sample sizes may be required in this group when looking at pacing pattern. Our findings differ to some extent from what is reported in healthy subjects and MS patients with mild disability (EDSS: 0–2.5) (16), showing that the normal pacing pattern involves a fast start during the first minute followed by a slowing and then a final "sprint" applying approximately the same speed as during the first minute. Goldman et al. (16) concluded that pacing pattern was dependent on disability level, since MS patients with moderate (EDSS: 3–4.0) and severe (EDSS: 4.5–6.5) disability were shown to start at a slower speed than the mild group and then slowed further during the test without acceleration during the last minute. However, this finding does not seem to be based on statistical analysis, but rather on visual inspection of curves, and the observed differences therefore may not be different in statistical terms. Furthermore, the differences between the studies may be explained by the smaller sample size in the study by Goldman et al. (16), especially in the range of EDSS >4.5 ($n=6$). Another explanation could be that the findings of Goldman et al. are based on 1 test session, whereas our findings are the mean of 3 test sessions, which may have reduced the variance in our data. In a recent paper, Motl et al. (14) expressed pacing pattern in terms of steps per minute. When expressed this way it was shown that steps per minute differed between disability groups (mild > moderate > severe), but was constant throughout the 6MWT in all disability groups. However, this measure does not take into account changes in step length and thereby walking speed, making these findings difficult to compare with the present study. Taken as a whole, the pacing pattern applied during the 6MWT seems robust across MS sub-groups, making the test equally applicable despite variations in disability, fatigue and MS subtype.

Limitations

This multi-centre study involved a convenience sample collected in 6 different centres, which may have induced a bias given differences in overall disability of patients, settings and assessors. The potential assessor bias was reduced by providing detailed and standardized testing manuals, and a help-desk. Although the severity of ambulatory dysfunction differed across participating centres, given that a convenience sample was assembled, statistical analyses did not detect any significant centre by time of day interaction effects, supporting the consistency of our findings (13). Another issue is the generalizabilty of our convenience sample, which may have a slightly higher age, a longer disease duration, a higher EDSS and more pronounced walking dysfunction than the general MS population. Despite our attempt to also include younger and less disabled patients, some of the participating rehabilitation centres may be biased due to national government or insurance regulations providing restrictions on the disability level required to attain a MS centre. Data from this study takes into account that testing in the morning (or at noon) could influence walking performance later that day and, as such, could have lowered performance during these tests. Regarding the HR measurements, we acknowledge that the relative HR is an estimate based on calculations of age-predicted HR_{max}, and, therefore, not the actual HR_{max}. In addition, the applied equations are based on data from healthy subjects and are not MS-specific, which may give an overestimation of the HR_{max}. A further limitation was that use of beta-blockers was not included as an inclusion criteria. Participating centres did report patient medication, and a review of these medical records did not reveal any participants receiving beta-blockers. However, most focus when registering these data was put on registration of immunomodulatory treatment, so it cannot be completely excluded that some participants were taking beta-blockers. Finally, a higher proportion of males were seen in the moderate and severe groups, which could have confounded the results. However, we did not find any time × group effects of gender, either on relative HR or on pacing pattern.

Conclusion

During the 6MWT aerobic intensity is moderate and unchanged throughout the day, with walking speed being fastest in the first minute and constant during the last 4 minutes in patients with MS. Aerobic intensity, but not pacing pattern, seem to be mildly influenced by disability, whereas fatigue and MS subtype do not have any effect.

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