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Whole-body cooling does not compromise muscle oxidative capacity in subjects with multiple sclerosis

Bert O Eijnde[a,*], Charly Keytsman[a], Inez Wens[a] and Dominique Hansen[a,b]
[a]*Rehabilitation Research Center (REVAL), Biomed, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium*
[b]*Heart Centre Hasselt, Jessa Hospital, Hasselt, Belgium*

Abstract.
BACKGROUND: Whole-body cooling improves exercise tolerance in patients with multiple sclerosis (pwMS). To be able to exercise at greater intensities and/or for longer durations with whole-body cooling, it should be examined whether this compromises skeletal muscle oxidative capacity (assessed by exercise-onset VO_2 kinetics).
OBJECTIVE: To study the impact of whole-body cooling on exercise-onset VO_2 kinetics in pwMS.
METHODS: From 12 pwMS (EDSS 3.5 ± 1.5) and 12 healthy age, BMI, and gender-matched subjects exercise-onset VO_2 kinetics (mean response time [MRT]) and body temperature were determined under normothermic and hypothermic (pre-exercise 60-min whole-body cooling) conditions during submaximal exercise testing (two 6-min constant-load exercise bouts). Moreover, heart rate, blood lactate content, expiratory volume and ratings of perceived exertion (RPE) were assessed during exercise.
RESULTS: Exercise heart rate (-7 ± 6 beats/min) and end-exercise body temperature ($-0.9 \pm 0.5^{\circ}$C) was significantly lower in hypothermic vs. normothermic conditions in both populations ($p < 0.05$). In pwMS exercise RPE was lower in hypothermic vs. normothermic condition ($p = 0.056$). No significantly different MRT was found between normothermic vs. hypothermic conditions in both populations.
CONCLUSIONS: Lowering body temperature prior to endurance exercise does not affect muscle oxidative capacity in pwMS, but lowers RPE, thus making it possible to prescribe exercises of greater intensity and/or longer duration.

Keywords: Multiple sclerosis, endurance exercise, oxygen uptake kinetics, oxidative capacity, whole-body cooling

1. Introduction

Patients with multiple sclerosis (MS) frequently suffer from fatigue. Such fatigue might inhibit participation into exercise interventions and lead to inactivity. In worst case this leads to elevated morbidity and mortality due to further deconditioning and development of cardiovascular and metabolic disease (Motl et al., 2011). Strategies to facilitate participation into exercise in patients with MS are therefore being explored.

Reducing body temperature in patients with MS leads to enhanced nerve conduction velocities and improved evoked potentials (Baker, 2002). Moreover, by applying whole-body cooling before exercise body core temperature increase during activity is reduced, thus minimizing heat-induced conduction difficulties (heat-sensitivity) in subjects with MS (Grahn et al., 2008; Reynolds et al., 2011; Skjerbaek et al., 2013; White et al., 2000). In patients with MS whole-body cooling leads to an

*Address for correspondence: Bert Op ‘t Eijnde, REVAL – Rehabilitation Research Center, Biomedical Research Institute (BIOMED) Hasselt University, Agoralaan building A, B-3590 Diepenbeek, Belgium. E-mail: bert.opteijnde@uhasselt.be.

improvement in daily physical activities and exercise tolerance (Grahn et al., 2008; Reynolds et al., 2011; White et al., 2000). As such and similar to other populations (Siegel et al., 2012), whole-body cooling could enable patients with MS to perform endurance exercises with greater intensities and/or for longer durations facilitating exercise intervention outcome.

However, although an improvement in neurologic function and body temperature control is anticipated when exercising under hypothermic conditions in patients with MS, reduced local skeletal muscle temperature leads to a reduction in oxygen uptake (VO_2) kinetics of this muscle (Shiojiri et al., 1997). Such slower VO_2 kinetics under hypothermic conditions can be explained by disturbances in oxidative reactions and/or decreased O_2 extraction in the working muscle (Shiojiri et al., 1997). It is well described that a preserved skeletal muscle oxidative capacity is mandatory to maintain exercise tolerance (Russ et al., 2004). As a result, such reductions in skeletal muscle oxidative capacity could prevent patients with MS from exercising at greater intensities (above the anaerobic threshold) and/or for longer durations (longer than 30 minutes) during whole-body cooling. Therefore, it should be examined whether whole-body cooling affects skeletal muscle oxidative capacity in subjects with MS.

In this study we examined skeletal muscle oxidative capacity in subjects with MS and healthy controls, when performing endurance exercise bouts in normothermic vs hypothermic condition. We hypothesized that by the application of whole-body cooling skeletal muscle oxidative capacity is compromised, and patients with MS thus are not able to exercise at greater intensities and/or for longer durations.

2. Methods

2.1. Participants

Twelve patients with multiple sclerosis (MS) were selected to participate in this study. Sample size of the population was based on sample sizes of similar studies in patients with MS in which significant effects were found (Grahn et al., 2008; Reynolds et al., 2011; Skjerbaek et al., 2013; White et al., 2000). Patients were included regardless of age and gender. These subjects had been diagnosed with MS for at least 12 months and were free from any other chronic disease. Twelve healthy subjects, matched for age, gender and body mass index, were included as a control group. These healthy subjects did not suffer from any chronic disease. Participants were informed about the experimental procedures, the nature and risks of measurements, and written informed consents of all participants were obtained. This study was approved by a local medical ethical committee of Hasselt University, Belgium.

2.2. Study design

This was a cross-sectional study in which subjects underwent exercise tests on two days, separated by one week. After obtaining information regarding Expanded Disability Status Scale (EDSS), medication intake, and level of physical activity (PASIPD) a constant-load exercise cycle ergometer test was performed to determine VO_2 kinetics during the first day (day 1). During the second day, the participants underwent one hour of whole-body cooling prior to the same exercise test (day 2).

2.3. Measurements

2.3.1. Level of physical activity

Daily physical activity, related to sports and recreational activities, household activities, transportation, labor activities, and sitting time, was evaluated by the 13-item Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) (van der Ploeg et al., 2007). From this questionnaire, the metabolic equivalent (MET) * hours/week was calculated.

2.4. Exercise test and exercise-onset VO_2 kinetics

Subjects performed a cardiopulmonary exercise test on an electronically braked cycle ergometer (eBike Basic, General Electric GmbH, Germany). Subjects were advised not to perform any exercise the day before testing, and only eat a light meal at least two hours prior to testing. Pulmonary gas exchange was continuously measured breath-by-breath with 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) was assessed breath-by-breath, after which these data were averaged every 10 sec. Heart rate was continuously monitored by 12-lead ECG. Predicted maximal heart rate was calculated by 220 – age.

During each exercise bout, capillary blood samples were obtained from the fingertip to analyze blood lactate concentrations (mmol/l), using a portable lactate analyzer (Accutrend Plus, Roche Diagnostics Limited,

UK) (Baldari, et al., 2009). At the end of each exercise bout ratings of perceived exertion (RPE) were scored by the subject on a 6–20 Borg scale.

Subjects were seated on cycle ergometer for three min to obtain resting data after having rested for 15 min in the laboratory. Next, subjects were instructed to cycle at 70 rpm, against a resistance corresponding to 25% (for patients with MS) or 35% (for healthy subjects) of predicted cycling power output (W_{max}), for six min (Hansen et al., 2013). After six min of cycling subjects remained seated on bike for an additional six min, after which a second 6-minute exercise bout was performed.

Predicted W_{max} was based on gender, age, body weight and height (Jones et al., 1985). A higher cycling resistance was selected in healthy subjects, as opposed to patients with MS, because a higher exercise capacity was anticipated in healthy controls, while relative exercise intensities during testing should be equal between groups to obtain valid comparisons of MRT between groups (Hansen et al., 2013).

Exercise-onset VO_2 kinetics were used as estimate of skeletal muscle oxidative capacity because these are significantly correlated with maximal VO_2, (Powers et al., 1985) and exercise-onset VO_2 kinetics are faster in skeletal muscle with predominantly slow-twitch fibers and/or with increased activation of oxidative muscle enzymes (Kowalchuk et al., 1990; Hughson, 2009). Moreover, exercise-onset VO_2 kinetics are significantly slowed in patients with MS (Hansen et al., 2013), and improved by exercise training (Murias et al., 2010). Thus it is generally accepted that exercise-onset VO_2 kinetics are sensitive for the evaluation of skeletal muscle oxidative capacity (Grassi, 2006).

Exercise-onset VO_2 kinetics were calculated algebraically and expressed as mean response time (MRT, see Fig. 1 for graphical clarification) (Hansen et al., 2013). The outcome parameter that is derived from this method correlates well with, and is not significantly different from, the time constant (Arena et al., 2003). Resting VO_2 was calculated as the VO_2 during the final min before exercise. Steady-state VO_2 was defined as the averaged VO_2 during the final min of cycling. The difference between rest VO_2 and steady-state VO_2, multiplied by exercise time (six min), was defined as the expected amount of VO_2 during exercise. However, 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 (Jones et al., 2003). The sum of VO_2 above resting level was defined as the actually achieved

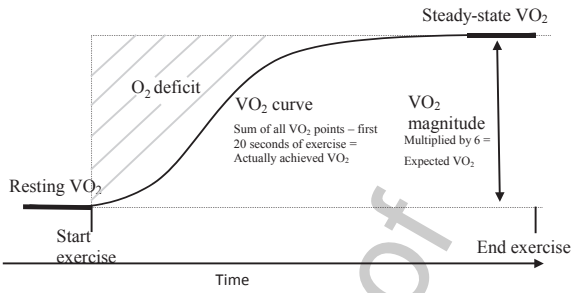

Fig. 1. Calculation of mean response time.

VO_2 during exercise. The oxygen deficit could then be calculated by: expected amount of VO_2 – actually achieved VO_2. Division of 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 sec, 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.

2.5. Whole-body precooling

Prior to the second exercise test participants wore a cooling vest and cap (Flexitherm, Life Enhancement Technologies LLC, China) during one hour while sitting in chair. The vest was connected to a cooler which pumped cold fluid through this vest and cap. During cooling body temperature was measured every 15 min by a classic mercury thermometer that was held under the tongue for four min. The temperature of the cooler was noted every time we measured body temperature to guarantee the same cooling temperature throughout the entire cooling session. The temperature of the cooler fluid lied between 7–13°C. Immediately after cooling participants performed the same exercise test with similar measurements.

2.6. Statistical analysis

All calculations were performed using the Statistical Package for the Social Sciences (IBM Corporation, USA). Data are expressed as means ± standard deviation. Shapiro-Wilk tests confirmed normal distribution of data. For non-time dependent variable comparisons (between healthy subjects and patients with MS), one-way analysis of variance was applied. To compare parameters between first and second exercise bout in patients with MS and healthy subjects, a paired-sample T–test was used. To compare normothermic

vs. hypothermic conditions in patients with MS and healthy subjects separately, 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).

3. Results

3.1. Subject characteristics

Only cycling power output was significantly different between groups (see Table 1, $p < 0.01$). Following medication was prescribed to the subjects: beta-blockers (1 in MS, 1 in control), statins (1 in MS, 1 in control), benzodiazepines (1 in MS, 1 in control), antiplatelets (1 in MS), anti-epileptics (1 in MS), interferons (3 in MS), anticholinergics (1 in MS), proton pump inhibitors (1 in MS), antifugal drugs (1 in MS), selective adhesion molecule inhibitors (2 in MS), ace-inhibitors (1 in control), antihistamines (1 in control), and meglitinides/biguanides (1 in MS, 1 in control).

3.2. Comparison between normothermic vs. hypothermic condition

During the first and second exercise bout, and when combining data from two exercise bouts, steady-state HR and steady-state %predicted maximal HR was significantly lower in hypothermic vs. normothermic conditions in healthy subjects and patients with MS ($p < 0.05$, see Table 2). Body temperature ahead of, and after, exercise was significantly lower in hypothermic vs. normothermic conditions in patients with MS and healthy subjects ($p < 0.05$).

In patients with MS steady-state ratings of perceived exertion were significantly lower in hypothermic vs. normothermic conditions during the second exercise bout ($p < 0.05$), and trends for reductions in ratings of perceived exertion from normothermic to hypothermic condition ($p = 0.056$) were found when combining data from two exercise bouts.

Table 1
Subject characteristics

	Healthy controls	MS patients
General characteristics		
N	12	12
Age (years)	50 ± 9	54 ± 7
N Males	5	4
Body height (cm)	173 ± 9	167 ± 7
Body weight (kg)	75 ± 17	69 ± 9
Body mass index (kg/m^2)	24.7 ± 3.3	24.8 ± 3.9
Disease characteristics ($n = 9$)$^{\#}$		
EDSS score	-	3.5 ± 1.5
Type of MS, n	-	
SPMS	-	2
RRMS	-	6
PPMS	-	1
PA score (MET/h/wk)	20.6 ± 12.7	13.6 ± 6.4
Cycling power output, W	58 ± 18	36 ± 9 *

Data are expressed as mean ± standard deviation and represent subject characteristics. *$p < 0.05$ compared to healthy subjects. $^{\#}$ information regarding disease characteristics were only obtained from 9 MS patients. Abbreviations: EDSS, Expanded Disability Status Scale; SPMS, secondary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; PA, physical activity; MET, metabolic equivalent.

3.3. Comparison between first and second exercise bout

Between the first and second exercise bout steady-state HR and steady-state % predicted maximal HR were significantly different within the hypothermic conditions in healthy subjects, but in patients with MS within the normothermic as well as within hypothermic conditions (see Table 2). Exercise blood lactate level was significantly different between bouts in healthy subjects in normothermic and hypothermic conditions ($p < 0.05$), but for patients with MS only in hypothermic condition ($p < 0.05$). Exercise ratings of perceived exertion were significantly different in normothermic condition in patients with MS between the first and second exercise bout ($p < 0.05$). Oxygen deficit was significantly different between first and second exercise bout in normothermic condition in patients with MS, but in the healthy subjects in normothermic and hypothermic conditions ($p < 0.05$).

3.4. Exercise-onset VO_2 kinetics

Mean response time (MRT) was significantly slower in patients with MS vs. healthy subjects in normothermic ($p < 0.05$) and hypothermic ($p < 0.05$) conditions (see Table 2). No significantly different MRT between normothermic and hypothermic conditions was found in patients with MS and healthy subjects. There was a significantly greater MRT in second vs. first exercise bout in patients with MS and healthy subjects, under normothermic and hypothermic conditions ($p < 0.05$).

3.4. Correlations

A significant moderate correlation was found between body weight ($r = 0.64$, $p < 0.05$) or % predicted maximal HR (indicator of exercise intensity) ($r = 0.69$,

Table 2
Exercise test data

	Healthy controls ($n=12$)		MS patients ($n=12$)	
	Control (day 1)	Precooling (day 2)	Control (day 1)	Precooling (day 2)
1st exercise bout				
Temperature before exercise (°C)	36.6 ± 0.5	36.3 ± 0.3	36.4 ± 0.4	36.1 ± 0.3*
HR rest (bpm)	78 ± 12	66 ± 6*	77 ± 8	64 ± 6*
VO_2 rest (ml/min)	307 ± 92	284 ± 92	289 ± 96	274 ± 79
Lactate rest (mmol/l)	2.5 ± 0.8	3.1 ± 1.1	2.9 ± 0.8	3.2 ± 0.9
Magnitude VO_2 (ml)	804 ± 200	816 ± 203	604 ± 140	629 ± 112
Steady-state VO_2 (ml/min)	1111 ± 261	1100 ± 264	892 ± 218	902 ± 141
Steady-state HR (bpm)	102 ± 9	93 ± 7*	105 ± 9	97 ± 9*
Steady-state % predicted max HR	60 ± 5	55 ± 5*	64 ± 6	58 ± 6*
Steady-state VE (l/min)	26.7 ± 7.3	26.9 ± 7.3	25.2 ± 5. 5	23.6 ± 4.2
Steady-state lactate (mmol/l)	3.0 ± 1.1	3.2 ± 0.9	2.7 ± 0. 9	3.3 ± 0.9
Steady-state Borg RPE	9.9 ± 1.4	10.2 ± 1.9	11.2 ± 2. 0	10.4 ± 2.4
O_2 deficit	290 ± 287	318 ± 256	453 ± 303	481 ± 289
Mean response time (sec)	20.4 ± 15.9	21.4 ± 13.7	43.7 ± 24.0	45.8 ± 27.6
2nd exercise bout				
VO_2 rest (ml/min)	319 ± 94	292 ± 69	274 ± 86	261 ± 50
Magnitude VO_2 (ml)	793 ± 194	817 ± 191	624 ± 167	650 ± 86
Steady-state VO_2 (ml/min)	1112 ± 257	1109 ± 246	899 ± 229	911 ± 129
Steady-state HR(bpm)	103 ± 8	97 ± 10*#	107 ± 10#	99 ± 10*#
Steady-state % predicted max HR	61 ± 5	57 ± 5*#	65 ± 6#	60 ± 6*#
Steady-state VE (l/min)	28.0 ± 6.9	27.3 ± 8.2	24.8 ± 5.5	24.5 ± 4.7
Steady-state lactate (mmol/l)	2.3 ± 0.7#	2.9 ± 1.2#	2.7 ± 0.9	2.9 ± 0.8#
Steady-state Borg RPE	10.2 ± 1.4	10.3 ± 2.0	12.1 ± 1.9#	10.3 ± 2.3*
O_2 deficit	505 ± 220#	594 ± 198#	625 ± 310#	609 ± 191
Mean response time (sec)	39.4 ± 16.6#	44.6 ± 14.3#	59.6 ± 26.4#	57.6 ± 22.0#
Temperature after exercise (°C)	36.7 ± 0.4	35.7 ± 0.3*	36.6 ± 0.4	35.8 ± 0.4*
Combined data: 1 + 2nd bout				
Rest VO_2 (ml/min)	313 ± 90	288 ± 78	282 ± 86	267 ± 61
Magnitude VO_2 (ml)	798 ± 196	816 ± 194	614 ± 151	639 ± 93
Steady-state HR (bpm)	103 ± 8	95 ± 9*	106 ± 9	99 ± 11*
Steady-state % predicted max HR	60 ± 5	56 ± 5*	64 ± 6	60 ± 8*
Steady-state lactate (mmol/l)	2.6 ± 0.8	3.1 ± 1.0	2.7 ± 0.8	3.1 ± 0.9
Steady-state VE (l/min)	27.3 ± 7.0	27.1 ± 7.7	25.0 ± 5.5	24.1 ± 4.3
Steady-state Borg RPE	10.0 ± 1.4	10.2 ± 1.9	11.6 ± 1.9	10.4 ± 2.4[b]
Steady state VO_2 (ml/min)	1111 ± 259	1104 ± 254	895 ± 222	906 ± 133
O_2 deficit	397 ± 233	456 ± 185	539 ± 290	545 ± 221
Mean response time (sec)	29.9 ± 13.3	33.0 ± 8.7	51.6 ± 23.5	51.7 ± 23.4

* represents difference between control test vs. precooling test within the same group ($p<0.05$). # represents difference between 1st and 2nd exercise bout within the same group ($p<0.05$). Abbreviations: MS, multiple sclerosis; VO_2, oxygen uptake; HR, heart rate; VE, expiratory volume; RPE, ratings of perceived exertion. [a]Data are expressed as mean ± standard deviation. [b]represents trend for reduction in ratings of perceived exertion ($p=0.056$)

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$p<0.05$) and decrease in body temperature as result of whole-body cooling in patients with MS (see Fig. 2). Changes in ratings of perceived exertion as result of whole-body cooling were not related to changes in MRT in patients with MS patients ($r=-0.08$; $p=0.81$).

4. Discussion

This study shows that whole-body cooling prior to endurance exercise in patients with MS does not affect exercise-onset oxygen uptake (Vo_2) kinetics, expressed as mean response time (MRT), but lowers ratings of perceived exertion. These data may indicate that skeletal muscle oxidative capacity is not compromised by whole-body cooling ahead of exercise in patients with MS in presence of greater exercise comfort, thus providing an opportunity to exercise at greater intensities and/or for longer durations.

Although whole-body cooling ahead of endurance exercise did not affect MRT, mild hypothermia was present after applying whole-body cooling. Body temperature at the end of exercise was -0.9 ± 0.5°C lower in total population in hypothermic vs. normothermic condition ($p<0.05$). Moreover, a significantly lower

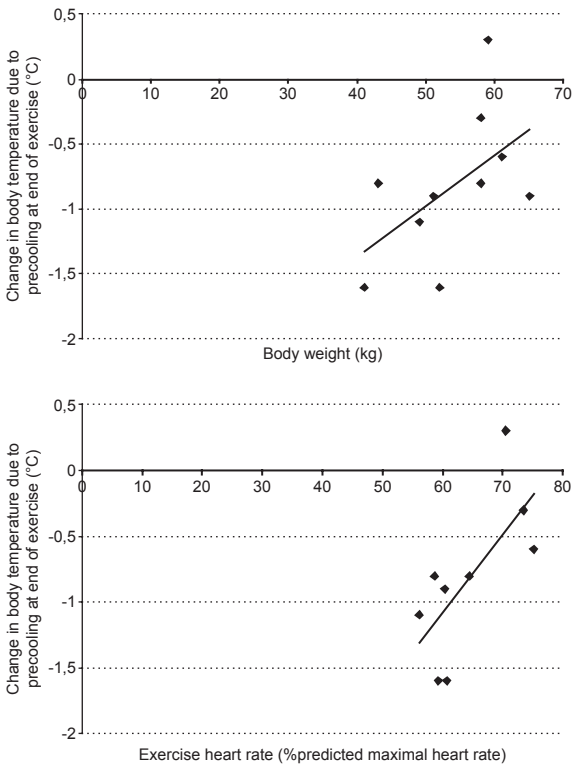

Fig. 2. Correlations.

exercise heart rate was observed in hypothermic vs. normothermic condition ($p < 0.05$). Whole-body cooling could lower heart rate because of cold-induced peripheral vasoconstriction, accompanied by an elevation in blood pressure (Doubt, 1991; McArdle et al., 1976). This could lead to baroreflex activation in which parasympathetic nervous system activation leads to bradycardia (Doubt, 1991; McArdle et al., 1976). Consequently, the lack of a change in MRT as a result of whole-body cooling probably was not due to limited effectiveness of the cooling protocol. Moreover, some subjects experienced the whole-body cooling procedure as unpleasant. So a more aggressive whole-body cooling protocol seemed not feasible in clinical practice.

Despite the absence of an effect of whole-body precooling on MRT in healthy subjects and patients with MS, lower ratings of perceived exertion during exercise in patients with MS were found in the hypothermic condition ($p = 0.056$). This confirms the fact that whole-body cooling prior to endurance exercise in patients with MS leads to greater physical comfort during such activity (Grahn et al., 2008; Reynolds et al., 2011; White et al., 2000). However, these lower ratings of perceived exertion were not related to changes in MRT (indicative for skeletal muscle oxidative capacity) in patients with MS ($r = -0.08$; $p = 0.81$). Thus follows that an improvement in physical comfort during exercise (or increased exercise tolerance as observed in previous studies) as result of whole-body cooling in patients with MS is probably not related to altered skeletal muscle oxidative capacity.

Our results contrast with previous findings in healthy subjects: a reduction in local skeletal muscle temperature would lead to reduced VO_2 kinetics of this muscle (Shiojiri et al., 1997). Even though the applied cooling protocol in this study was at a local muscle level and much more vigorous compared to ours, it seems fair to conclude that whole-body hypothermic conditions do not impair skeletal muscle oxidative capacity.

In this study, a significant moderate correlation was found between exercise %predicted maximal heart rate (which indicates exercise intensity) and the effect of whole-body cooling in patients with MS ($r = 0.69$, $p < 0.05$). The lower the exercise %predicted maximal heart rate, and thus degree of exercise intensity, the greater the reduction in body temperature was as result of whole-body cooling in patients with MS. During exercise, heat is produced from the conversion of metabolic energy into mechanical and thermal energy. However, when exercise is intense, a doubling in heat production occurs (Gonzalez-Alonso, 2012). Therefore, smaller reductions in body temperature as result of whole-body cooling could be anticipated during exercises of greater intensity, due to greater heat production.

A moderate correlation was also found in patients with MS between body weight and reductions in body temperature during whole-body cooling ($r = 0.65$, $p < 0.05$). A greater reduction in body temperature could be achieved by whole-body cooling in patients with MS who were leaner. An explanation for this correlation remains presently speculative.

Examining the impact of medication intake on MRT, and influence of whole-body cooling, is difficult in the present study because only to few patients (maximally up to three) a certain drug was prescribed. However, it has been shown that beta-blocker intake significantly slows exercise-onset VO_2 kinetics, while ACE-inhibitor intake exerts the opposite effect (Kowalchuk et al., 1990; Dayi et al., 2004).

4.1. Study limitations

A mercury thermometer was used to measure (core) body temperature orally. Such assessment of body temperature is however not always valid

(Mazerolle et al., 2011). Rectal temperature devices are more valid for body core temperature assessment. Moreover, the thermometer was not calibrated before each assessment. However, evidence for a reduced body core temperature is present because of a significantly reduced heart rate during exercise in the whole-body cooling condition. This study was also limited by the small sample size. In future studies, it could be interesting to obtain skeletal muscle biopsies to assess muscular oxidative capacity directly, and the impact of hypothermia during exercise.

5. Conclusions

Lowering body temperature prior to endurance exercise does not compromise exercise-onset VO_2 kinetics in patients with MS, but leads to lower ratings of perceived exertion. Exercising at greater intensities and/or for longer durations during whole-body cooling may thus be possible to patients with MS.

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Declaration of interest

None declared.

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