Environmental temperature and exercise modality independently impact central and muscle fatigue among people with multiple sclerosis

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Abstract

Background: Heat sensitivity and fatigue limit the ability of multiple sclerosis patients to participate in exercise.

Objective: The purpose of this study was to determine the optimal aerobic exercise parameters (environmental temperature and exercise modality) to limit exercise-induced central and muscle fatigue among people with multiple sclerosis.

Methods: Fourteen people with multiple sclerosis with varying levels of disability completed four randomized exercise sessions at 65% of the maximal volume of oxygen: body-weight supported treadmill cool (16°C), body-weight supported treadmill room (21°C), total-body recumbent stepper cool and total-body recumbent stepper room. Maximum voluntary contraction, electromyography, and evoked contractile properties were collected from the more affected plantar flexors along with subjective levels of fatigue, body temperature and perceived level of exertion.

Results: Exercise in cooler room temperature increased maximum voluntary contraction force ($p = 0.010$) and stabilized body temperature ($p = 0.011$) compared to standard room temperature. People with multiple sclerosis experienced greater peak twitch torque ($p = 0.047$), shorter time to peak twitch ($p = 0.035$) and a longer half relaxation time ($p = 0.046$) after total-body recumbent stepper suggestive of less muscle fatigue.

Conclusion: Cooling the exercise environment limits the negative effects of central fatigue during aerobic exercise and using total-body recumbent stepper (work distributed among four limbs) rather than body-weight supported treadmill lessens muscular fatigue. Therapists can titrate these two variables to help people with multiple sclerosis achieve sufficient exercise workloads.

Keywords: Muscle fatigue, aerobic exercise, electromyography, triceps surae, plantar flexor, heat sensitivity

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tailored exercise protocols so that PwMS can achieve optimal exercise workloads.7

Exercise-induced fatigue could be due to impaired motor drive from the central nervous system (CNS) (central fatigue) or reduced capacity from within the muscle.8,9 Research supports the interplay of both mechanisms. Demyelination of motor pathways,10 impaired thermoregulation, and transient increase in symptoms with passive heat exposure11 point to a central origin. However, decreased muscle peak twitch (PT) force output and prolonged half-relaxation time (HRT) during fatiguing electrical stimulation of the tibialis anterior in PwMS11 is suggestive of peripherally induced fatigue within the muscle.11,12

Aerobic exercise is typically performed on a treadmill but can be adapted for PwMS who have balance difficulties by using seated or recumbent methods. For example, Pilutti et al.13 compared the safety and tolerability of the total body recumbent stepper (TBRS) to the body-weight supported treadmill (BWST) and found that 12 weeks of TBRS and BWST training reduced perceived fatigue, although PwMS reported a more positive experience with the TBRS.13 It is conceivable that distributing the workload between all four limbs, PwMS would have less excessive lower limb fatigue. Choosing the appropriate exercise modality (seated or upright) and cooling the temperature of the exercise environment are simple methods that therapists and patients can employ in order to titrate aerobic exercise parameters to make training achievable.

The primary aim of this study was to determine the acute effects of combining temperature (‘cool’, 16°C or 'room', 21°C) and exercise modality (BWST or TBRS) on lower extremity central fatigue (maximum voluntary contraction (MVC)), muscle fatigue (evoked contractile properties), body temperature, and perceived levels of fatigue. We hypothesized that: (a) exercising in a cooler temperature would prevent post-exercise decreases in MVC and electromyography (EMG) and (b) due to distributed workload between all four limbs, PwMS would have less perceived fatigue following the TBRS compared with the BWST. In order to understand potential mechanisms, our exploratory aims were to evaluate the relationships between exercise-induced changes in body temperature, subjective fatigue, the extent of clinical disability, and changes in neuromuscular performance.

Methods
Following approval of the Health Research Ethics Board (ref. no. 14.102), participants were recruited from outpatient rehabilitation services and the local MS clinic. From these participants, 14 PwMS (10 females) were included; they all met the following inclusion criteria: (a) diagnosis using the McDonald criteria;14 (b) a negative Physical Activity Readiness Questionnaire (PAR-Q)15 screening; (c) being relapse-free during the past three months; (d) taking no medication that affects heart response to exercise; (e) having no musculoskeletal impediment to exercise; and (f) scoring greater than 24 on the Montreal Cognitive Assessment (MoCA).16

Experimental design
During the first session, demographic and MS-related data were collected (age, years since diagnosis, Fatigue Impact Scale (FIS)).17 PwMS self-reported their degree of heat sensitivity using a visual analogue scale (VAS); zero being not at all sensitive and 100 being extremely sensitive. Lower limb strength was tested using manual muscle testing, spasticity using the Modified Ashworth Scale and self-selected walking velocity using an instrumented walkway (Protkinetics, Havertown, Pennsylvania, USA).

BWST and TBRS graded maximal exercise tests (GXTs) were performed (Figure 1(a)) and maximal volume of oxygen (VO2max) was used to assign 60–65% of heart rate (HR) reserve for 30 min of aerobic exercise (including a five-minute warm-up and cool down). The participants completed four randomized exercise sessions, one week apart either on TBRS or BWST in a temperature controlled room at 16°C (cool) or 21°C (room); BWSTcool, BWSTroom, TBRScool, TBRSroom (Figure 1(a)). Rate of perceived exertion (RPE; Borg Scale (10-point)) and HR were recorded at intervals 1, 15, and 30 min during exercise. Prior to each exercise session, participants were prepared for EMG (Figure 1(b)) and performed isometric contractions of the plantar flexors at various low intensities as a warm-up. Before and after exercise, participants performed two MVCs, received posterior tibial nerve stimulation, rated their perceived fatigue on a 100 mm VAS, and had body temperature recorded using a tympanic thermometer (Thermoscan, Braun, Kronberg, Germany).
Maximal exercise tests

\( V_{O2max} \) test was performed on both the BWST using 10% body weight support (Sport Art T625M/T52 MD-Rehabilitation Commercial Treadmill, USA) and the TBRS (NuSTEP T4r Recumbent stepper, Michigan, USA), according to guidelines adapted from stroke best practices. Height, weight, age, resting HR, and blood pressure were taken prior to the GXT. The metabolic cart (Moxus Metabolic Systems, AEI Technologies, Inc., Pittsburgh, Pennsylvania, USA) was calibrated and expired air was analyzed breath-by-breath using a mask (HR: Polar V800, Polar Electro Oy, Professorintie 5, FI-90440 Kempele, Finland).

Measurement of plantar flexor muscle force and electromyography

Participants sat with their weaker leg flexed (i.e. 90° at the hip, knee, and ankle joints) and foot mounted in a modified boot apparatus equipped with a load cell, and performed two five-second MVCs. Participants were told to push into plantar flexion as hard as possible for five seconds. Force was sampled at 1 kHz, amplified (\times1000) and averaged. EMG was recorded via surface 10 mm electrodes (MediTrace Pellet Ag/AgCl, Graphic Controls Ltd., Buffalo, New York, USA) placed longitudinally 2 cm apart over the lateral gastrocnemius (LG) and soleus (SOL) muscles of the weaker leg (determined by manual muscle test) and a ground electrode was secured on the lateral epicondyle of the femur. Signals were amplified (1000×), filtered using a Butterworth filter with a pass-band of 10–500 Hz and analog-digitally converted at a sampling rate of 1000 Hz (Biopac MP150WSW, Biopac Systems Inc., Holliston, Mississippi, USA). Data were recorded and analyzed (Acknowledge 4.1, Biopac Systems Inc.). MVC forces were measured as the peak force recorded during each contraction. For the LG and SOL muscles, root mean square (RMS) EMG was calculated over 500 ms about the peak force amplitude during the MVC for each muscle.

Assessment of evoked contractile properties

To assess twitch contractile properties in LG and SOL muscles; electrical stimulation was applied to the posterior tibial nerve via Ag/AgCl electrodes placed in the popliteal fossa (cathode) and over the tibial tuberosity (anode). Current pulses (200 ms duration, 100–400 mA) were delivered via a constant current stimulator (DS7AH; Digitimer, Welwyn Garden City, Hertfordshire, UK). Stimulation intensity was increased until PT torque of LG and SOL plateaued. Evoked contractile properties included:

- (a) PT torque
- (b) time to peak twitch (TPT), and
- (c) HRT – the time it took for the PT torque to reduce to half of its maximum amplitude. Lower PT and longer TPT are indicative of fatigue and lower efficiency of fiber cross-bridge cycling, respectively.

Statistical analysis

To determine whether the exercise conditions were at the equivalent aerobic intensity, repeated measures analysis of variance (ANOVA) for exercise condition (TBRS, BWST) and temperature (cool, room) were performed on HR, power output, and RPE averaged across three time points (1 min, 15 min, 30 min) during the 30 min of aerobic exercise. A repeated measures ANOVA for exercise condition (TBRS, BWST) by temperature (cool, room) was also performed on change scores (CS) (post minus pre; MVC\(_{cs}\), RMS EMG\(_{cs}\), PT\(_{cs}\), TPT\(_{cs}\),...)
Exercise modality affected evoked contractile properties

Following BWST there was evidence of plantar flexor fatigue. There was a significant main effect of exercise modality on plantar flexor PTcs, (Figure 4; $F_{(1,11)} = 5.11$, $p = 0.047$, $n^2_p = 0.338$) with decreased PT amplitude following BWST ($-0.71 \pm 0.982$ Nm) and an increase following TBRS ($2.48 \pm 1.173$ Nm). There was also a significant main effect of exercise modality on TPTcs ($F_{(1,11)} = 5.92$, $p = 0.035$, $n^2_p = 0.372$) with prolonged TPT following BWST ($0.004 \pm 0.009$ ms) and shortened TPT following TBRS ($-0.019 \pm 0.007$ ms). Further, there was a significant main effect of exercise modality on HRTcs, ($F_{(1,11)} = 5.21$, $p = 0.046$, $n^2_p = 0.343$) with shortened HRT following exercise on a BWST ($-17.80 \pm 2.845$ ms) compared to exercise on TBRS ($-5.89 \pm 4.487$ ms).
Table 2. Raw data for voluntary and evoked contractile properties.

| Measure          | Exercise | Temp | Pre- (n=11) | Post- (n=11) |
|------------------|----------|------|-------------|--------------|
| MVC (Nm)         | BWST     | Cool | 89.81 (± 62.41) | 100.3 (± 66.83) |
| MVC (Nm)         | TBRs     | Cool | 95.18 (± 53.19) | 108.9 (± 61.89) |
| MVC (Nm)         | BWST     | Room | 112.3 (± 68.66) | 101.1 (± 55.72) |
| MVC (Nm)         | TBRs     | Room | 98.90 (± 62.72) | 93.68 (± 64.79) |
| LG EMG (RMS)     | BWST     | Cool | 0.063 (± 0.0359) | 0.065 (± 0.0402) |
| LG EMG (RMS)     | TBRs     | Cool | 0.062 (± 0.0334) | 0.072 (± 0.0488) |
| LG EMG (RMS)     | BWST     | Room | 0.076 (± 0.0446) | 0.062 (± 0.0404) |
| LG EMG (RMS)     | TBRs     | Room | 0.082 (± 0.0582) | 0.072 (± 0.0593) |
| HRT (ms)         | BWST     | Cool | 121.2 (± 25.96) | 110.3 (± 21.22) |
| HRT (ms)         | TBRs     | Cool | 117.9 (± 22.37) | 104.6 (± 27.80) |
| HRT (ms)         | BWST     | Room | 132.8 (± 34.50) | 108.1 (± 28.23) |
| HRT (ms)         | TBRs     | Room | 107.4 (± 26.94) | 108.9 (± 24.20) |
| PT (Nm)          | BWST     | Cool | 15.09 (± 9.644) | 13.76 (± 7.101) |
| PT (Nm)          | TBRs     | Cool | 14.09 (± 6.245) | 16.76 (± 10.12) |
| PT (Nm)          | BWST     | Room | 15.07 (± 6.702) | 14.99 (± 8.750) |
| PT (Nm)          | TBRs     | Room | 14.46 (± 6.835) | 16.75 (± 9.719) |
| TPT (ms)         | BWST     | Cool | 0.15 (± 0.0213) | 0.14 (± 0.0196) |
| TPT (ms)         | TBRs     | Cool | 0.16 (± 0.0255) | 0.15 (± 0.0347) |
| TPT (ms)         | BWST     | Room | 0.13 (± 0.0504) | 0.14 (± 0.0255) |
| TPT (ms)         | TBRs     | Room | 0.17 (± 0.0229) | 0.14 (± 0.0274) |

Maximal Voluntary Contraction (MVC); Lateral Gastrocnemius (LG); Electromyography (EMG); Newton Meter (Nm); Root Mean Square (RMS); Temperature (Temp); Half Relaxation Time (HRT); Peak Twitch (PT); Time to Peak Twitch (TPT); milliseconds (ms); Total body recumbent stepper (TBRS); Body-weight supported treadmill (BWST).
There was no effect of temperature on PTcs, TPTcs or HRTcs, and no significant interaction between temperature and exercise modality (data not shown).

**Effects of exercise modality on perceived level of fatigue and body temperature**

There were significant main effects of exercise modality and environmental temperature on body tempcs (Table 3; $F_{(1,9)} = 7.61$, $p = 0.022$, $n_p^2 = 0.458$, $F_{(1,9)} = 10.08$, $p = 0.011$, $n_p^2 = 0.528$, respectively). Greater increases in body temperature were observed following exercise in room temperature ($0.33 \pm 0.104^\circ C$) compared to cool temperature ($-0.15 \pm 0.123^\circ C$). There was a greater increase in body temperature following TBRS ($0.29 \pm 0.094^\circ C$) compared to BWST ($0.025 \pm 0.126^\circ C$). There was no significant main effect of exercise modality or environmental temperature on perceived level of fatiguecs and no significant interaction of exercise modality and temperature (data not shown).

**Relationship between body temperature, degree of heat sensitivity and neuromuscular performance**

Since there was little change in body temperature in the cool condition, changes in body temperature in the room temperature conditions were compared to the corresponding post-exercise MVC torque. Higher body temperature was correlated with declines in post-exercise MVC torque in BWST (Figure 5; $r = 0.65$, $p = 0.028$) and a nearly significant negative relationship in TBRS ($r = 0.58$, $p = 0.075$). There was no relationship between body temperature and evoked contractile properties. Nether was there a relationship between perceived

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**Table 3.** Raw data for change in body temperature (data are reported as mean ($M$) ± standard deviation (SD))

| Measure      | Exercise | Temp      | Pre- ($n = 11$) | Post- ($n = 11$) |
|--------------|----------|-----------|----------------|-----------------|
| Body temp ($^\circ C$) | BWST     | Cool      | 36.65 ($\pm 0.454$) | 36.45 ($\pm 0.780$) |
| Body temp ($^\circ C$) | TBRS     | Cool      | 36.65 ($\pm 0.418$) | 36.74 ($\pm 0.559$) |
| Body temp ($^\circ C$) | BWST     | Room      | 36.49 ($\pm 0.287$) | 36.73 ($\pm 0.402$) |
| Body temp ($^\circ C$) | TBRS     | Room      | 36.35 ($\pm 0.462$) | 36.78 ($\pm 0.524$) |

BWST: Body-weight supported treadmill; TBRS: Total body recumbent stepper; Temp: temperature.
fatigue, degree of heat sensitivity, MVC, EMG, or evoked contractile properties.

**Relationship between MS-related disability and neuromuscular performance**

As expected, higher EDSS scores were significantly correlated with lower MVC ($r = -0.54$, $p = 0.045$), lower LG ($r = 0.62$, $p = 0.022$), SOL RMS EMG ($r = -0.66$, $p = 0.013$), and greater baseline perceived fatigue ($r = 0.67$, $p = 0.012$).

**Discussion**

The main findings of the current study were (a) with large effect sizes, a cooler environment (16°C) limited elevation of body temperature and increased plantar flexor MVC torque and protected against decrements in EMG after exercise, suggesting an effect of temperature on CNS drive and (b) exercising on a recumbent stepper using all four limbs enhanced plantar flexor contractile properties as compared to treadmill training, suggesting an effect of exercise modality on the excitation-contraction coupling of the muscle. These findings occurred despite the fact that the exercise interventions were matched for workload and participants perceived the exercise on the TBRS as more strenuous than the BWST. Finally, the neuromuscular performance measures, specifically MVC and RMS EMG of the lower limb, correlated with clinical disability (EDSS), strengthening their usefulness as biomarkers of subtle MS-related sensorimotor change.

**Environmental temperature and central drive**

In the present study, exercising in room temperature (raising body temperature) led to decreased MVC torque and LG EMG, with no concomitant changes in evoked contractile properties post-exercise, pointing to CNS mechanisms underlying these changes. Other studies support such a theory. When PwMS were exposed to passive body heating, walking, force generation capacity, and increased fatigue perception were affected. Furthermore, passively-heated PwMS had decreased corticospinal excitability as shown via increased resting motor threshold and decreased motor evoked amplitude. Increased body temperature may also alter action potential propagation in demyelinated or partially myelinated axons causing reduced conduction velocity and/or block. In the present study, exercising in cool temperature enhanced MVC torque with no change in LG EMG. The cool temperature may have alleviated heat-induced stress on the CNS, allowing for improved MVC performance.

Exercising in warm or cool environments, and rate of heat storage in the body, have been postulated to differentially activate an anticipatory response that regulates skeletal muscle power output and motor unit recruitment through afferent sensory inputs to the brain. Other studies have shown that, in PwMS, water immersion precooling before arm-leg ergometry exercise stabilized core temperature and improved 25-foot walk performance and that the use of cooling suits improved walking speed and lower-limb strength. Decreasing body heat storage, especially during exercise, may allow for improved CNS function and enhanced neuromuscular performance. Since comfort is likely important for exercise compliance, the longer-term effects (over hours and days) of temperature and fatigue on neuromuscular measures and functional tasks is an important area for future study.

**Exercise modality**

Based on our findings that BWST resulted in lower PT force and longer TPT, the BWST may create impaired excitation-contraction coupling of the plantar flexor muscles, indicating greater muscle fatigue, compared to the TBRS. Conversely, the TBRS facilitated the excitation-contraction coupling of the plantar flexor muscles demonstrated by increased PT force and shorter TPT. The enhancement of plantar flexor muscle contractile properties following the TBRS may be related to exercise-induced post-activation potentiation (PAP); enhanced calcium kinetics, myosin phosphorylation, and reduced muscle stiffness after non-fatiguing contractions. Biomechanically, the distributed workload between the upper and lower limb muscles required to perform the TBRS at a comparable physiological workload as submaximal BWST exercise, that predominately engages muscles of the lower limb, may help to explain our findings. For those with fatigue and heat sensitivity, choosing the TBRS in a cooler environment may allow patients to reach optimal aerobic exercise training levels.

**Perceptions of fatigue**

In a clinical setting, the patient’s subjective report of heat sensitivity and fatigue during exercise may be used when titrating aerobic training intensity. However, in this study, perceived fatigue following exercise was not related to objective measures of central or muscular fatigue, illustrating a disconnect between psychological vs physiological aspects of fatigue in PwMS following exercise. This disconnect suggests that subjective reports may not be sensitive enough to gauge heat-related fatigue. Dawes et al. showed that PwMS reporting general fatigue could

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train at comparable levels to those without fatigue suggesting that clinicians, in addition to obtaining subjective reports, should focus on objective markers of exercise intensity such as HR to gauge exercise parameters. Our findings suggest that, at least within a training session, the TBRS may be more tolerable especially for those with higher levels of MS-related disability. However, due to the importance of the exercise-induced stress response that is incurred from challenging exercise,27 transition to the BWST may be warranted as training progresses.

Detecting subclinical changes in neuromuscular performance
We found not only that there was an inverse relationship between EDSS score and MVC force and EMG of the plantar flexor muscles, but also the neuromuscular measures detected subtle deficits sometimes unbeknownst to the participant. Others have demonstrated that MVC, central activation,28 and evoked contractile properties10 are decreased in PwMS compared to controls and there is a negative correlation between EDSS and measures of corticospinal excitability.29 In a disease where most of the degeneration is subclinical and where lesions can outnumber clinical relapses 10 to one,30 there are opportunities to incorporate neuromuscular performance outcomes as potential biomarkers of MS disease progression.

Study limitations
This study makes important strides in developing tailored aerobic exercise interventions for PwMS. However, there were some limitations. Even though effect sizes were moderate to large, the sample size was small and because of inability to complete the BWST, participants with EDSS >6 were underrepresented.

Body temperature was measured using the tympanic method. The most sensitive methods to measure thermoregulation and changes in core temperature are invasive, and are recorded using rectal and esophageal techniques. However, the aim of the present study was to use methods that could be easily incorporated into clinical practice and inform best practice guidelines for clinical exercise prescription.

Conclusions
Cooling the temperature of the training environment lessens central fatigue while choosing a modality that distributes workload among four limbs (TBRS) rather than two (BWST) limits muscular fatigue. Therapists can modify these parameters in order to achieve optimal aerobic exercise training levels among PwMS.

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