**Increased postural sway in persons with multiple sclerosis during short-term exposure to
warm ambient temperatures**

Paula Y.S. Poh^{*1}, Amy N. Adams¹, Mu Huang², Dustin R. Allen², Scott L. Davis², Anna S. Tseng³,
and Craig G. Crandall¹

¹, *Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital and UT
Southwestern Medical Center, Dallas, TX, USA;* ², *Department of Applied Physiology and
Wellness, Southern Methodist University, Dallas, TX, USA;* ³, *Neurology Consultants of Dallas,
Texas Health Presbyterian Hospital, Dallas, TX, USA*

*present address: Warfighter Performance Department, Naval Health Research Center, San Diego, CA, USA

Address for correspondence:

Dr. Craig G. Crandall

Institute for Exercise and Environmental Medicine

Texas Health Presbyterian Hospital Dallas

7232 Greenville Ave

Dallas, TX 75231

craigcrandall@texashealth.org

214-345-4623 (O)

214-345-4618 (F)

ABSTRACT

Background: Multiple sclerosis (MS) is a neurological disease marked by demyelination and axonal loss. Individuals with MS experience increases in clinical signs and symptoms during heat exposure. **Objective:** To test the hypothesis that moderate heat exposure adversely affects postural sway in individuals with MS. **Methods:** Ten individuals with relapsing-remitting MS (50 ± 8 y) and nine controls (47 ± 10 y) were examined under a Thermal and a Time Control trial. Following a 30min thermoneutral baseline (25°C , 30% relative humidity (RH)), stand tests randomized with eyes open and closed, was performed. For Thermal, subjects were first exposed to 60min of heating (40°C , 30%RH) followed by 60min of cooling (20°C , 30%RH). For Time Control, subjects remained in a thermoneutral environment throughout. Stand tests were repeated at consistent times in both trials. **Results:** No difference in skin and core temperatures between groups were observed for any trial ($P > 0.05$). During heating, postural sway was higher in MS relative to control subjects (eyes open, $P = 0.03$; eyes closed, $P = 0.011$). No differences in postural sway, regardless of eye status, were observed during the Time Control trial for either group ($P > 0.05$). **Conclusion:** These data demonstrate that exposure to a moderate heating environment increases postural sway in patients with MS.

Key words: hyperthermia, balance, multiple sclerosis, postural sway, force plate, environmental chamber

INTRODUCTION

Individuals with multiple sclerosis (MS) often experience transient increases in the frequency of clinical signs and symptoms during heat exposure with subsequent increases in body temperature [1, 2]. Disturbances in neurological function due to heat exposure in MS, clinically defined as Uhthoff's phenomenon, are short in duration (less than 24 h), and are typically reversible upon removal from the heat exposure and/or by cooling the individual [3]. Uhthoff's phenomenon was quantitatively modeled in patients with MS by demonstrating impaired ocular motor function during heat stress and restoration of ocular motor function with subsequent cooling [4]. The physiological processes involved in this heat sensitivity are poorly understood, but are likely due to increased susceptibility of demyelinated axons to elevated temperature [2], and pore closure of voltage gated sodium channels and potassium efflux that compromise action potential depolarization leading to conduction slowing or even blockage [5]. Notably, heat exposure can negatively influence MS patient safety and functional capacity, including the ability to perform activities of daily living.

Individuals with MS often have poor postural control [6, 7], underlying an increased risk of falling [8,9], which is further compromised by prior heat exposure that increases core body temperature by 0.5°C [10]. Importantly however, it is unknown whether postural stability is compromised in persons with MS during relatively acute heat exposure that elevates mean skin temperature, but not core temperature. If acute heat exposure that does not appreciably change internal temperature impairs postural stability in individuals with MS, these individuals would be at a greater risk of falling and fall related injuries during short-term exposure to conditions of elevated environmental temperature [11, 12].

Thus, the purpose of this study was to test the hypothesis that moderate heat exposure that does not increase core temperature will compromise postural stability in persons with MS to a greater extent relative to healthy individuals without MS. Such findings would provide further knowledge regarding the effects of acute heat exposure on individuals with MS.

MATERIALS and METHODS

Subjects. Ten individuals with relapsing-remitting MS (9 women, 1 man; mean $\pm$ SD: age, 50 ± 8 y, mass, 75 ± 16 kg, height, 167 ± 9 cm) and nine healthy controls (8 women, 1 man; age, 47 ± 10 y; mass, 66 ± 9 kg; height, 163 ± 10 cm) volunteered to participate in this study. Persons with MS received medical clearance from their doctor, had not relapsed within the prior 6 months, were not taking any corticosteroids, and had an Expanded Disability Status Scale of 3.7 ± 1.5 . Both persons with MS and healthy control subjects were non-smokers, free of any known cardiovascular, respiratory, or metabolic diseases and not taking any related medications. Written informed consent was obtained from all subjects prior to their participation in the study. All procedures were approved by the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital of Dallas Institutional Review Board for Human Subjects, and all data were de-identified to maintain confidentiality.

Experimental Protocol. Both healthy control subjects (CON) and subjects with MS underwent two randomized trials, one under heat stressed (Thermal) conditions, and one under normothermic (Time Control) conditions. Trials were performed at the same time of day, within subject, and separated by a minimum of 24 h. All participants refrained from strenuous physical

activity for 24 h, as well as from caffeinated drinks and alcohol for 12 h prior to the experimental visits. Participants were also instructed to arrive at least 3 h postprandial. Prior to the start of both trials, urine specific gravity (CON: 1.015 ± 0.009 ; MS: 1.015 ± 0.006) was measured in duplicate using a handheld refractometer (Atago Inc., Bellevue, WA, USA) to confirm all subjects were adequately hydrated prior to each trial. Pre- and post-trial nude body mass was measured using a scale accurate to 0.1 kg (Health-O-Meter Professional Scales, McCook, IL, USA), which was used to assess whole-body sweat loss as a result of the thermal exposure.

A graphical representation of the experimental procedures is illustrated in Figure 1. Following a 30 min seated baseline period in a thermoneutral environment (BASE; 25°C, 30% relative humidity (RH)), a baseline series of stand tests was performed. For the Thermal trial, subjects were then exposed to a warm environment (HEAT; 40°C, 30% RH), upon which stand tests were repeated after 60 min of heating. With heating continuing, subjects were then exposed to 5 min of mechanical fanning (air velocity = $2 \text{ m}\cdot\text{sec}^{-1}$), in an attempt to reduce skin temperature, after which another series of stand tests were performed. The fan was then turned off, and subjects were exposed to a cool environment (COOL; 20°C, 30% RH) with stand tests performed after 60 min of cooling. For the Time Control trial, stand tests were conducted at the same time points as the Thermal trial, but in a normothermic environment (25°C, 30% RH) throughout the entire period. Subjects remained in a seated position throughout both trials, with the exception of during the stand tests. Blood pressure, heart rate, and mean skin and core temperatures were recorded, while seated, prior to each set of stand tests, and during the stand tests.

Measurements. Trials were conducted in a 120 square foot environmental chamber in which ambient temperature and relative humidity were tightly controlled. Intestinal temperature was measured as an index of core temperature with a telemetric temperature-sensing pill (HQ Inc. Palmetto, FL, USA) that was swallowed a minimum of 1 h prior to data collection. Mean skin temperature was measured as the indicated weighted average of 6 thermocouples attached to the skin surface on the abdomen, (14%), calf (11%), chest (22%), lower back (19%), thigh (13%) and upper back (21%). Heart rate was obtained from an electrocardiogram (GE Healthcare, Milwaukee, WI, USA) that was interfaced with a cardiometer (CWE, Ardmore, PA, USA). Blood pressure was measured by automated auscultation of the brachial artery (Tango+ SunTech Medical, Morrisville, NC, USA), with continuous measurements obtained non-invasively using photoplethysmography (Finometer Pro, FMS, Amsterdam, Netherlands).

Stand tests were conducted on a low-profile pressure-sensing mat (Tekscan, Inc., Boston, MA) that measured the distance travelled from the center of gravity, an index of postural sway. For each designated time point (e.g., BASE, HEAT, COOL), six stand tests were performed, three with the eyes closed and three with the eyes opened [13-15], which were introduced in a randomized order based on a coin flip. For stand tests with the eyes open, subjects focused at an eye-level target on the adjacent wall ~2 m away [16]. Each stand test was 30 sec in duration with ~30 sec of seated recovery between subsequent stand tests.

Data Analysis. Thermal and hemodynamic data were collected with data acquisition software (Biopac MP150, Santa Barbara, CA, USA) at a sampling frequency of 50 Hz and subsequently

converted into 1 min averages for data analysis. To ensure a representative assessment of postural stability, averaged responses of the last 20 sec from the three stand tests per eye condition were analyzed. In contrast to our expected outcome, the 5 min fanning component did not reduce mean skin temperature, perhaps due to the level/duration of the heat stress not being sufficient to cause sweating. Given the absence of a desired skin cooling effect, data during the fanning condition were not further analyzed nor are they presented.

Statistical Analysis. For each thermal condition and each eye state, responses between groups were analyzed with a two way mixed-model ANOVA with main factors of group (MS and CON) and time (BASE, HEAT, COOL). Based upon hypothesized differences, apriori pairwise comparisons were performed via the Holm-Šidák approach, which adjusts the P-value for multiple comparisons. Statistical analyses were performed using SigmaPlot (Systat Software Inc., San Jose, CA, USA), and results are reported as mean $\pm$ SD.

RESULTS

Thermal Variables. For both trials, and in both subject groups, whole-body water loss was small (≤ 0.37 kg), and not different between groups ($P > 0.05$). During the Thermal trial, mean skin temperature during HEAT was elevated from BASE, and subsequently returned to values not different from BASE during COOL for both subject groups ($P > 0.05$; Table 1). Core temperature was unaffected by the Thermal trial for both the CON and MS groups. For the Time Control trial, there were no differences in mean skin or core temperatures between subject groups or across time ($P > 0.05$; Table 1).

Postural Sway. During the Thermal trial, postural sway was elevated during HEAT when compared to BASE for the MS group only, regardless of whether the eyes were open ($P = 0.024$) or closed ($P = 0.051$; Figure 2, Panel A). This increase in postural sway, during the HEAT stand tests, in the MS group were higher relative to the CON group, for both eyes open (MS: 19.1 ± 14.5 cm, CON: 11.0 ± 5.5 cm, $P = 0.03$), and eyes closed (MS: 29.6 ± 18.5 cm, CON: 14.8 ± 6.0 cm, $P = 0.011$) conditions (see Figure 2, Panel A). Notably, during the Thermal trial, the increase in postural sway distance in the MS group returned to BASE values during COOL. There were no differences in postural sway across the Time Control trial within each group, or at any stage between groups, for either the eyes open or eyes closed conditions ($P > 0.05$; Figure 2, Panel B).

Hemodynamic Variables. For the Thermal trial, seated mean arterial pressure was not different between groups or stages, with the exception of this variable being elevated during the COOL stage for CON, relative to BASE and HEAT ($P < 0.02$; Table 1). Regardless of whether the eyes were open or closed, during standing for the Thermal trial, mean blood pressure decreased during HEAT in both groups (Figure 3, Panel A), with no differences in blood pressure between groups at any stage ($P > 0.05$). For the Time Control trials, there was a general increase in mean blood pressure across time during standing, without any differences in blood pressure responses between groups at any stages ($P > 0.05$; Figure 3, Panel B).

Seated heart rates (prior to stand tests) during Thermal and Time Control trials were generally greater in MS at all stages ($P < 0.05$; Table 1). During standing, regardless of eye status or Thermal or Time Control trials, heart rate was elevated in MS ($P \leq 0.015$; Figure 4, Panels A

and B). Moreover, also regardless of eye status, heart rate was elevated in both groups during HEAT of the Thermal trial relative to BASE ($P \leq 0.045$), but not during the Time Control trial ($P > 0.05$).

DISCUSSION

The novel findings of this study revealed that short-term exposure to warm ambient temperatures increased postural sway in individuals with MS relative to CON during stand tests with both the eyes open and closed. Our findings revealed that acute hyperthermic exposure has a detrimental effect on postural stability in patients with MS relative to CON, regardless of the eye status. Of clinical importance, heat exposure that increases skin temperature, but not core temperature is encountered in everyday life, which was simulated via the experimental model.

While mean skin and core temperature responses were similar between subject groups, heart rates were elevated at all time points for both experimental trials in the MS group (Figure 4, Panels A and B). This could indicate altered cardiovascular function in the MS group [17-20], though no group differences in blood pressures were observed. Overall, these data support the hypothesis that moderate hyperthermic exposure, without changes in core body temperature, is detrimental to postural stability in persons with MS, which we propose can increase their susceptibility to falls. Subsequent environmental cooling alleviated these heat-induced decrements in the MS group.

In the subjects with MS, postural stability for either eye condition was unchanged during Time Control trial, while sway distance increased during HEAT of the Thermal trial (Figure 2,

Panel A), which supports our hypothesis that acute heat exposure compromises postural stability in patients with MS. As further support, no changes in postural stability were observed in CON during either experimental trial. As explained by Uhthoff's phenomenon, patients with MS often experience a worsening of neurological symptoms when body temperature increases, as would occur during elevated ambient temperatures [1, 21, 22]. Based on self-report surveys, heat sensitivity in patients with MS was highly correlated with the most incapacitating symptoms of MS, such as fatigue, pain and concentration problems [22]. Further, Romberg et al. [10] reported that poor postural control in patients with MS was further compromised by prior heat exposure sufficient to increase average core temperature by 0.5°C and above, which underlie their risk of falling. The present study extends those observations by demonstrating that in the absence of core temperature changes, postural stability is adversely affected in persons with MS during acute exposure to an ambient temperature sufficient to elevate mean skin temperature (Table 1).

The mechanisms responsible for heat sensitivity are multifaceted since symptoms can vary greatly across patients with MS [1, 22]. One possible scenario is the increased susceptibility of demyelinated axons of the central nervous system to elevated temperature, which results in slower nerve conduction velocity [2] as a result of pore closure of voltage gated sodium channels and potassium efflux [5]. Disruptions affecting conduction within the central nervous system of such patients can potentially impair thermoregulatory effector responses, which have led physicians and health care providers to advise patients with MS to minimize their exposure to elevated temperatures [21]. However, due to the absence of an increase in core temperature

(< 0.5°C) during HEAT of the present study, it is unlikely that the heat affected central neurons since the temperature of those nerves probably did not increase, although this was not verified.

Another possible component to the heat sensitivity phenomenon in patients with MS is cardiovascular disturbances resulting from underlying autonomic dysfunction [17-20]. Arterial blood pressures during the HEAT stand tests of the Thermal trial, with both the eyes open and closed, similarly decreased between MS and CON (Figure 3, Panel A). Based on these data, it appears unlikely that the increase in postural sway seen in the group with MS was related to hypotension. However, cerebral perfusion was not measured, and perhaps the reductions in blood pressure upon standing resulted in decreased cerebral blood flow, in the individuals with MS, that may have contributed to the observed increase in postural sway. Although information regarding the effects of MS on the control of cerebral blood flow and autoregulation is sparse, Rashid et al. [23] reported alterations in cerebral perfusion in patients with MS.

Core body temperature was measured with an ingestible transmitter pill that resided within the gastrointestinal system. Gastrointestinal temperatures can sometimes lag temperature measurements from other locations, such as the esophageal [24]. Thus, it remains possible that slight increases in other measures of core body temperature increased during the Thermal challenge, despite the absence of an increase in gastrointestinal temperature. That said, we do not expect this occurred given prior findings reporting an absence of esophageal temperature changes during passive heat exposure for a similar duration, as the present protocol, in environmental temperature and humidity conditions more extreme than that imposed on the present subjects [25, 26]. However, those studies were conducted in individuals without MS, and thus we cannot exclude the possibility of slight elevations in body

core temperature from other regions during the Thermal trial in the patients with MS. Even if such occurred, we anticipate those increases to be very small and inconsequential, particularly relative to the large elevations in skin temperature.

CONCLUSION

Based on the combination of the lack of change in postural sway during both trials in the CON group and during the Time Control trial in the group with MS, the increased in sway observed in the MS group during HEAT resulted from the warm ambient conditions. These findings suggest that patients with MS have decreased postural stability during increased ambient temperatures that do not increase core temperature, regardless of if the eyes are open or closed, which potentially increases the risk of falling when exposed to hot environments. Moreover, during stand tests with both the eyes open and closed in the Thermal trial, postural sway returned to BASE values following exposure to a cool environment in these subjects with MS (Figure 2, Panel A). Thus, if heat exposure is unavoidable, exposure to a cool environment (e.g., air-conditioned areas, ice water baths, and perhaps misters) can attenuate or reverse heat-induced postural instability.

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DISCLAIMER

All experiments were performed at the Institute for Exercise and Environmental Medicine. All authors contributed to the conception and design of the experiment, as well as data collection. All authors contributed to the interpretation of the data and to revision the manuscript for important intellectual content. All authors have approved the final version of the manuscript, and declare no conflicts of interest, financial or otherwise.

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FIGURE LEGENDS

Figure 1. Graphical illustration of the experimental procedures. Following instrumentation, subjects underwent a 30 min baseline period in a thermoneutral environment (BASE; 25°C, 30% relative humidity, (RH)). During the Thermal trial, subjects were then exposed to a warm environment for 60 min (HEAT; 40°C, 30% RH); fanning for 5 min (data not reported, see methods); and a cool environment for 60 min (COOL; 20°C, 30% RH). Note: indicators are not drawn to scale. During Time Control trials, subjects remained in a thermoneutral environment throughout (25°C, 30% RH). Arrows denote when stand tests were performed for both Thermal and Time Control trials.

Figure 2. Mean ($\pm$ SD) sway distance for eyes open (Column I) and closed (Column II) stand tests during Thermal (Row A) and Time Control (Row B) trials in persons with MS and healthy control (CON) subjects. *, different from BASE for the indicated condition and group ($P \leq 0.051$). Note that during the Time Control trial, subjects were not exposed to HEAT or COOL, rather those labels reflect the responses at the same time as the indicated conditions during the Thermal trial.

Figure 3. Standing mean ($\pm$ SD) arterial pressures during Thermal (Panel A) and Time Control (Panel B) trials in persons with MS and healthy control (CON) subjects during stand tests; no differences between subject groups. *, different from BASE for the indicated condition and group, $P \leq 0.034$. Note that during the Time Control trial, subjects were

not exposed to HEAT or COOL, rather those labels reflect the responses at the same time as the indicated conditions during the Thermal trial.

Figure 4. Standing mean ($\pm$ SD) heart rate during Thermal (Panel A) and Time Control (Panel B) trials in persons with MS and healthy control (CON) subjects during stand tests. For each trial and stage, heart rate was elevated in MS relative to CON (main effect of group: $P \leq 0.015$). *, different from BASE for the indicated condition and group, $P \leq 0.045$. Note that during the Time Control trial, subjects were not exposed to HEAT or COOL, rather those labels reflect the responses at the same time as the indicated conditions during the Thermal trial.

Figure 1

	Instrumentation	BASE	HEAT	FAN	COOL					
Thermal	25°C, 30% RH	25°C, 30% RH	40°C, 30% RH		20°C, 30% RH					
Time Control			25°C, 30% RH							
Minutes	-15	0	...	30	...	90	...	95	...	155
				↑		↑		↑		↑

Figure 2

A. THERMAL

B. TIME CONTROL

Figure 3

A. THERMAL

B. TIME CONTROL

Figure 4

A. THERMAL

B. TIME CONTROL

Table 1 Thermal and Hemodynamic Variables

		BASE	HEAT	COOL
Mean Skin Temperature (°C)				
Thermal	MS	32.4 ± 0.7	36.2 ± 0.5 [*]	31.7 ± 0.9
	CON	32.0 ± 1.3	36.5 ± 1.0 [*]	30.6 ± 3.4
Time Control	MS	32.4 ± 0.5	32.4 ± 0.7	32.3 ± 0.7
	CON	32.6 ± 0.4	32.6 ± 0.5	32.5 ± 0.4
Core Temperature (°C)				
Thermal	MS	37.3 ± 0.3	37.4 ± 0.2	37.6 ± 0.2
	CON	37.4 ± 0.3	37.4 ± 0.3	37.5 ± 0.3
Time Control	MS	37.3 ± 0.2	37.3 ± 0.3	37.4 ± 0.4
	CON	37.6 ± 0.5	37.3 ± 0.3	37.4 ± 0.3
Mean Arterial Pressure (mmHg)				
Thermal	MS	95.8 ± 12.2	93.1 ± 8.1	97.5 ± 10.2
	CON	88.2 ± 7.8	89.2 ± 7.0	95.4 ± 9.2 ⁺
Time Control	MS	95.6 ± 9.8	95.6 ± 11.6	97.6 ± 9.3
	CON	88.9 ± 7.4	91.5 ± 9.9	92.6 ± 10.1
Heart Rate (beats·min ⁻¹)				
Thermal	MS	81.9 ± 12.4 [^]	91.0 ± 14.3 [^]	78.6 ± 11.2 [^]
	CON	65.7 ± 9.7	75.5 ± 11.6	67.5 ± 11.6
Time Control	MS	76.6 ± 8.7 [^]	72.2 ± 9.6	72.5 ± 10.1 [^]
	CON	67.7 ± 8.4	64.4 ± 6.8	61.8 ± 5.5

Seated mean (± SD) skin temperature, core temperature, arterial pressure, and heart rate during Time Control and Thermal trials in individuals with MS and healthy control (CON) subjects. THERMAL VARIABLES: There were no differences between subject groups at each time period. ^{*}, different from BASE and COOL within the indicated group, $P < 0.05$. HEMODYNAMIC VARIABLES: [^], different from CON for that condition and trial, $P < 0.05$; ⁺, different from BASE and HEAT for the CON group, $P \leq 0.02$. Note that during the Time Control trial, subjects were not exposed to HEAT or COOL, rather those labels reflect the responses at the same time as the indicated conditions during the Thermal trial.