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Lindsay Horton, Amy Conger, Darrel Conger, Gina Remington, Teresa Frohman, Elliot
Frohman and Benjamin Greenberg
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HIGHLIGHTED TOPIC | *Mechanisms and Modulators of Temperature Regulation*

Thermoregulation in multiple sclerosis

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Davis SL, Wilson TE, White AT, Frohman EM. Thermoregulation in multiple sclerosis. *J Appl Physiol* 109: 1531–1537, 2010. First published July 29, 2010; doi:10.1152/japplphysiol.00460.2010.—Multiple sclerosis (MS) is a progressive neurological disorder that disrupts axonal myelin in the central nervous system. Demyelination produces alterations in saltatory conduction, slowed conduction velocity, and a predisposition to conduction block. An estimated 60–80% of MS patients experience temporary worsening of clinical signs and neurological symptoms with heat exposure. Additionally, MS may produce impaired neural control of autonomic and endocrine functions. This review focuses on five main themes regarding the current understanding of thermoregulatory dysfunction in MS: *1*) heat sensitivity; *2*) central regulation of body temperature; *3*) thermoregulatory effector responses; *4*) heat-induced fatigue; and *5*) countermeasures to improve or maintain function during thermal stress. Heat sensitivity in MS is related to the detrimental effects of increased temperature on action potential propagation in demyelinated axons, resulting in conduction slowing and/or block, which can be quantitatively characterized using precise measurements of ocular movements. MS lesions can also occur in areas of the brain responsible for the control and regulation of body temperature and thermoregulatory effector responses, resulting in impaired neural control of sudomotor pathways or neural-induced changes in eccrine sweat glands, as evidenced by observations of reduced sweating responses in MS patients. Fatigue during thermal stress is common in MS and results in decreased motor function and increased symptomatology likely due to impairments in central conduction. Although not comprehensive, some evidence exists concerning treatments (cooling, precooling, and pharmacological) for the MS patient to preserve function and decrease symptom worsening during heat stress.

demyelination; core temperature; sweating; skin blood flow; fatigue

MULTIPLE SCLEROSIS (MS) is a disabling progressive neurological disorder affecting ~400,000 individuals in the United States. The pathophysiology of MS results in a disruption or loss of axonal myelin in the central nervous system (CNS), leading to the formation of scar tissue (sclerosis). MS is thought to involve a number of autoimmune injury cascades that appear to be dependent on the interaction of complex epigenetic and environmental factors. Immune responses in individuals with MS are skewed toward a proinflammatory state, resulting in inflammation, demyelination, and ultimately loss of axons and disorganization of normal tissue architecture within the CNS (23). Demyelination is associated with corresponding changes in axonal physiology, including a loss of saltatory properties of electrical conduction, reduction in conduction velocity, and a predisposition to conduction block. These pathophysiological mechanisms underlie the myriad of symptoms (Table 1) in individuals with MS and are contingent on the neuroanatomic localization of lesions (23).

Autonomic dysfunction involving the genitourinary, gastrointestinal, cardiovascular, and thermoregulatory systems is commonly observed in MS (29). In addition to autonomic dysfunction, the majority of MS patients experience transient and temporary worsening of clinical signs and neurological symptoms in response to a number of factors, the most prominent of which are increased ambient or core body temperature and exercise. However, the assessment and understanding of autonomic dysfunction in individuals with MS is problematic due to the variability of early clinical symptoms and the heterogeneity in the clinical course over time (Fig. 1). With these limitations in mind, this review will focus on our current understanding of the thermoregulatory dysfunction in MS while characterizing five main topical themes: *1*) heat sensitivity; *2*) central regulation of body temperature; *3*) thermo-

Table 1. *Common symptoms of multiple sclerosis*

Most Common Symptoms	Less Common Symptoms
Fatigue	Speech disorders
Walking (gait), balance, and coordination problems	Swallowing problems
Bowel dysfunction	Headache
Dizziness and vertigo	Hearing loss
Pain	Seizures
Emotional changes	Tremor
Spasticity	Respiration/breathing problems
Numbness	Itching
Bladder dysfunction	
Vision problems	
Sexual dysfunction	
Cognitive dysfunction	
Depression	

Based on information from National Multiple Sclerosis Society (Ref. 73).

regulatory effector responses; *4*) heat-induced fatigue; and *5*) countermeasures to improve function in MS patients during a thermal stress.

HEAT SENSITIVITY IN MS

The earliest medical reports of thermal sensitivity in MS are derived from Charles Prosper Ollivier d'Angers who noted in 1824 that a hot bath induced numbness in the right leg and reduced feeling and dexterity in the hands of a patient with MS (56). However, Wilhelm Uhthoff's description of this phenomenon occurring after a hot bath or with exercise in MS patients with a history of optic neuritis has most commonly been cited as the landmark observation of the pathophysiological principle of temperature-induced conduction block in demyelinated axonal segments (Uhthoff's phenomenon) (77). It is estimated that 60–80% of the MS population experience transient and temporary worsening of clinical signs and neurological symptoms as a result of elevated body temperature by immersion in warm water (41–43°C) or exposure to infrared heating lamps (27, 46, 50, 51).

Symptom worsening can result from passive heat exposure, exercise (increase in metabolism), or a combination of heat exposure and increases in metabolism (exercise-heat stress). Both physical (walking, running, driving, writing, etc.) and cognitive (memory retrieval, processing speed, multitasking, etc.) functions can be impaired by heat exposure, greatly impacting overall patient safety as well as the ability of individuals with MS to perform routine activities of daily living, even in mildly affected individuals (57, 59). Symptom worsening has been reported with exercise (78), hot shower (81), and sunbathing (2). Even fluctuations in circadian body temperature from the morning to the afternoon can elicit changes in symptoms (62).

In the past, physicians and health care providers instructed MS patients to minimize their exposure to high ambient temperatures and to avoid exercise or intense physical work in order to avoid symptom worsening. However, lack of exercise often results in deconditioning, reduced functional capabilities, increased risk of injury, and less weight-bearing movement, which has consequences on bone and mineral metabolism (59, 88). Evidence now indicates that exercise is beneficial to individuals with MS by improving fitness and sense of well being, reducing fatigue, and increasing strength and safety of

walking and should be incorporated into their overall disease management plan (57).

Typically, deficits caused by increases in temperature are reversible by removing heat stressors and allowing subsequent cooling. Davis et al. (15) quantified Uhthoff's phenomenon during indirect whole body heating and its reversibility with the subsequent application of active cooling by objectively measuring horizontal eye movement velocities in a group of MS patients with internuclear ophthalmoparesis, an abnormality characterized by the slowing of the eye moving toward the nose (adduction) during horizontal eye movements. The speed of horizontal eye movements in MS patients with internuclear ophthalmoparesis was slowed from baseline when core body temperature was raised ~0.8°C with whole body heating and returned to baseline following 1 h of whole body cooling (Fig. 2) (15).

The precise mechanisms for impaired neural function in demyelinated axons due to increases in temperature are not completely understood but are likely due to a combination of structural and physiological changes within axons in the CNS (75). With demyelination, increases in temperature can affect the propagation of action potentials. Increased temperature may also influence the electrical properties of the nerve fiber by increasing the refractory period (partly mediated by potassium channel activation and sodium channel inactivation), which

Onset of MS   **Course of MS**
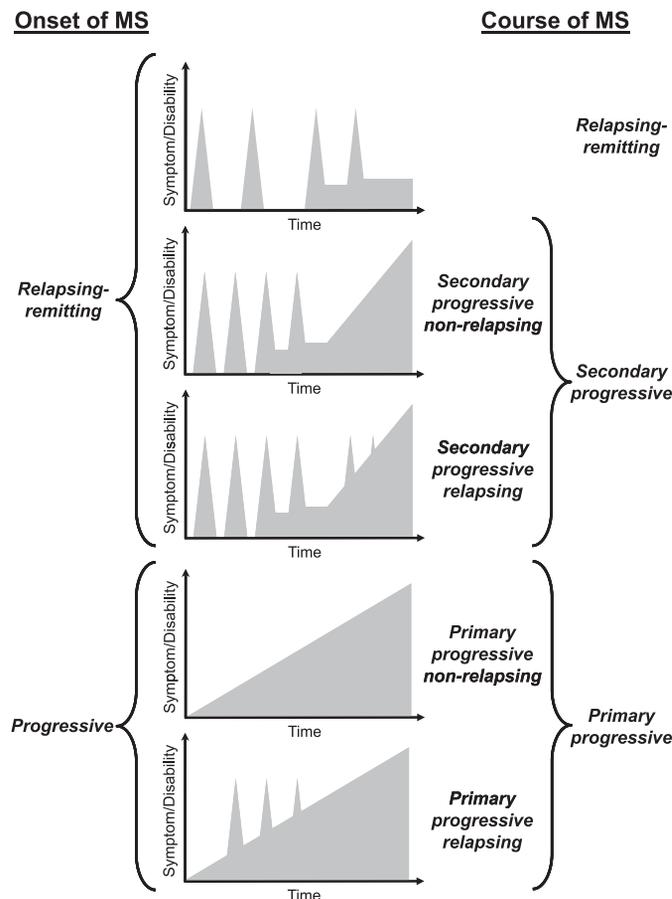

Fig. 1. Clinical courses of multiple sclerosis (MS). Adapted from Confavreux and Vukusic (11) with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health.
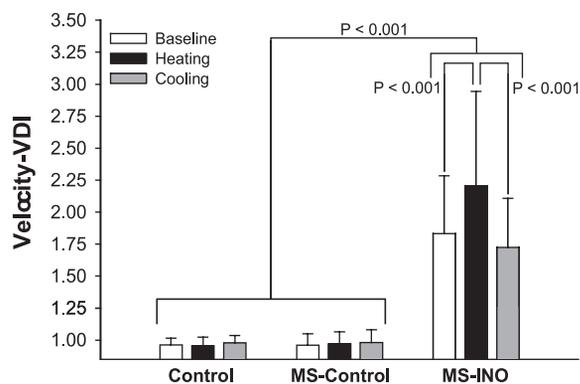
Fig. 2. Data from healthy controls (Control; $n = 8$), MS patients without internuclear opthalmoparesis (MS-Control; $n = 8$), and MS patients diagnosed with internuclear ophthalmoparesis (MS-INO; $n = 8$) showing ocular function responses [velocity-versional dysconjugacy index (VDI)] during whole body heat stress (increase internal temperature $\sim0.8°C$) and subsequent whole body cooling (return to normothermic baseline). A significant slowing ($P < 0.001$) of horizontal eye movements (increasing velocity-VDI) was observed in MS patients with INO during whole body heating. However, ocular function was restored to preheating baseline with subsequent whole body cooling. Data are expressed as means $\pm$ SD. Reproduced from Davis et al. (15) with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health.

surpass the action potential-generating processes (sodium channel activation) (32).

Demyelination reduces the axon's safety factor, defined as the ratio of the current available to stimulate a node of Ranvier to the minimal amount of current needed to excite a node of Ranvier (72). In healthy, myelinated axons, the safety factor for saltatory conduction ranges from a factor of 3–7 (i.e., the current available to stimulate the node is 3–7 times greater than the current needed to excite the node) (76). Compared with myelinated axons, demyelinated axons have a much lower safety factor that can approach a critical value (~1), resulting in failure to generate an action potential across the next node of Ranvier and ultimately culminating in conduction block. Increased temperature further reduces the safety factor, thereby influencing the threshold of current to excite an axon, the rate at which current is generated, and the total amount of current available (13, 14, 66). This combination of demyelination and increased temperature (even as little as $0.5°C$) in individuals with MS can cause nerve conduction block (60). The degree of conduction block is a factor of both the magnitude of myelin loss and the time since the demyelination has occurred, suggesting that individuals with more severe cases of MS are at greater risk for developing conduction block (72). In some cases, conduction can be restored to injured axons during periods of disease remission, as some remyelination may occur. However, conduction in these areas of repair is not optimal and is therefore prone to failure (72). Often, areas of axonal injury reach a point in which repair is no longer possible, and the functional deficit becomes permanent.

CENTRAL REGULATION OF BODY TEMPERATURE IN MS

Compounding temperature-related nerve conduction problems, individuals with MS may have impaired neural control of autonomic and endocrine functions (30). Thermosensitive neurons of the preoptic anterior hypothalamus process afferent thermal information (central and peripheral) to integrate and direct autonomic thermoeffector responses (6, 63). Areas of the

sympathetic nervous system (hypothalamic area and interomediolateral columns of the spinal cord) that are responsible for controlling thermoregulatory function are susceptible to disease-related pathology in individuals with MS (1).

Hypothermia has been documented in a small number of MS patients (18, 42, 44, 74, 83, 87) with core temperatures ranging from 30 to $35°C$. Hypothermia can be profound but tolerated in MS patients. Lesions within the CNS, specifically the hypothalamus, may impair the homeostatic control of body temperature in individuals with MS and allow for atypical fluctuations in body temperature (45). Hypothermia may be more common than reported and be indicative of more severe disease (87). Fluctuations in body temperature can be problematic for MS patients when infections have been masked due to the absence of a typical fever response, resulting in serious medical conditions.

HEAT-INDUCED FATIGUE IN MS

Fatigue is a frequent and sometimes debilitating symptom in MS, present in nearly 70% of MS patients (22, 39). Fatigue, evidenced by reports of decreased motor function and increased symptomatology, worsens during thermal stress in individuals with MS. Heat stress has also been shown to induce muscle fatigue in healthy individuals (35, 48, 55). Due to its relative importance, increased fatigue associated with thermal stress in MS will be briefly discussed in this review. A recent review by Marino (47) provides a more detailed discussion of fatigue associated with thermal stress in MS.

Physiological fatigue is defined as the failure to maintain an expected work output (5). Patients with MS experience decreased maximal motor unit firing (61), alterations in motor unit recruitment (52), and excitation-contraction coupling (69) likely contributing to this physiological fatigue. However, these mechanisms do not fully explain fatigue in MS (malaise or lack of energy). It is generally accepted that centrally mediated fatigue, an inability to sustain central drive to spinal motoneurons (24), plays a greater role than peripheral factors in MS fatigue (43). It has been hypothesized that heat-related fatigue is also a form of central fatigue (55). Using transcranial magnetic stimulation, a noninvasive technique used to measure conduction properties of the corticospinal tract and excitability of the motor cortex, White et al. (84) demonstrated that fatigue induced by raising core temperature by $0.8°C$ via indirect whole body heating in MS patients produces a corresponding decrease in central motor conduction time and cortical excitability. These results most likely occurred as a result of slowed or blocked conduction in demyelinated lesions in the CNS (28, 31) associated with alterations in central activation (58, 70).

THERMOREGULATORY EFFECTOR RESPONSES IN MS

Increases in skin blood flow and sweating are the primary heat dissipation mechanisms in humans. Without these dissipation mechanisms, internal temperature would reach the upper "safe" limit within 10 min of moderate exercise (36). Based on the severe consequences that may occur with elevated body temperature in MS, control of skin blood flow and sweating are crucial for patient safety (81).

Lesions affecting conduction within the CNS of MS patients can potentially impair thermoregulatory effector responses to eccrine sweat glands. This is evidenced by previous studies

that report reduced sweating responses in MS patients (10, 53, 79). In the aforementioned studies, abnormal sweating responses were identified by using quinizarin powder placed on the skin of individuals followed by exposure to a heat stress. Quinizarin powder, normally gray in color, changes to a deep blue when exposed to sweat. The intensity of the change in color provides a visual estimate of sweating (19, 41). However, this technique cannot quantitatively identify differences in sweating or determine whether diminished sweating is due to a decreased number of active sweat glands, altered innervation of the glands, and/or reduced output from activated glands. Using a more quantitative approach, Davis et al. (17) transdermally delivered a cholinergic agonist (pilocarpine) to activate eccrine sweat glands independent of the CNS. Diminished sweat function was identified in individuals with MS, and this reduction was not caused by reduced sweat gland recruitment but was due to reduced sweat gland output per gland (Fig. 3). Even though sweating was induced locally by an agonist, it is possible that CNS impairments or even neuronal loss within the descending sudomotor pathways due to the disease process contributed to the observations of diminished sweat function in these patients (1, 79). Impaired sweat function appears to occur more frequently in MS patients with more severe cases of disease (10).

Quantification of sweat function during heat stress has produced conflicting findings. Saari and colleagues (65) have reported impaired sweating responses in the lower limbs of MS patients compared with healthy controls during a 15-min passive heat stress of the upper torso. Alternatively, no sweating impairments were reported in a group of MS patients with optic neuritis exposed to the same passive heating paradigm (64). In both of the aforementioned studies, the magnitude of the heat stress was minimal (increase in core temperatures of 0.1°C), and thus it is uncertain whether thermoregulatory effector responses were even engaged. Davis et al. (16) have documented sweating and cutaneous blood flow responses in individuals with MS when internal temperature was increased ~1.0°C. Whole body heating was performed by placing MS patients in a tube-lined suit through which 48°C water was perfused to increase skin temperature, leading to the increase in internal temperature. The suit covered the entire body surface area except the head, hands, feet, and regions of skin blood flow and sweating assessment (dorsal forearm). Because the suit was not in contact with the regions of skin where skin blood flow and sweat rate were assessed, responses from these areas were not affected by local heating but rather were due to reflex-induced neural modulation in response to changing internal body temperature. Sweating responses to heat stress were significantly lower in individuals with MS compared with healthy controls and may have been due to impairments in neural control of sudomotor pathways or neural-induced changes in eccrine sweat glands. Interestingly, larger increases in cutaneous vasodilation to whole body heating were observed in MS patients compared with healthy controls and suggest neural control of skin blood flow is intact and may compensate for impairments in sweating in an attempt to adequately dissipate heat.

To address the potential for decreases in sweating function being due to detraining or deadaption, Davis et al. (17) trained seven MS patients for 15 wk to improve their sweat function. Aerobic exercise training alters central gain to initiate sweating at a lower body temperature (33, 71) and also increases maximal sweating responses (12, 90). Despite 15 wk of training, this group of MS patients improved neither sweat gland recruitment nor sweat output per gland. Taken together, these data indicate that MS affects thermoregulatory effector responses and that adaptive thermoregulatory responses to exercise training typically observed in healthy individuals are not seen in MS patients, suggesting impaired CNS control in MS patients.

COUNTERMEASURES TO IMPROVE FUNCTION IN MS PATIENTS DURING THERMAL STRESS

To reduce the potentially detrimental effects of heat sensitivity, several treatment strategies have been employed to allow individuals with MS to participate in activities of daily living, including exercise. Simple behavioral strategies are used to minimize heat exposure, such as performing work or exercise outside during the early morning or late evening when temperatures are cooler. A small number of studies have reported potential benefits using cooling strategies that are convenient methods available to most MS patients such as cold showers, applying ice packs, the use of regional cooling devices, and drinking cold beverages (3, 7, 26, 67, 80).

Precooling (cooling before heat exposure) presents another practical and strategic treatment option for minimizing the consequences of heat stress in MS patients. Immersing the lower limbs in cool water (i.e., cold tap water in a bath tub) creates negative heat storage before thermal stress or the initiation of exercise. White et al. (86) demonstrated that water immersion precooling (cooling the lower limbs in 20°C water
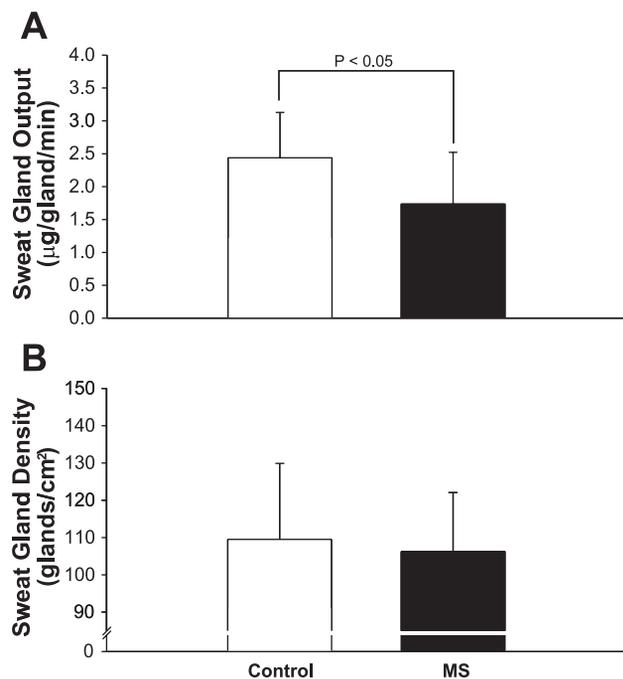
Fig. 3. Data from control and MS patients showing decreased sweat gland output per gland ($P < 0.05$) compared with matched, healthy controls following iontophoresis of pilocarpine, a cholinergic agent (A). No differences were observed in the number of sweat glands recruited between healthy controls and MS patients (B). Data are expressed as means ± SD. Modified from Davis et al. (17).

for 30 min before physical activity) was effective in preventing gains in core temperature during physical work and may minimize heat-induced conduction difficulties in MS patients (Fig. 4). Precooling allows the lower limbs to effectively serve as heat "sinks" in order to blunt internal temperature increases and decrease reliance on eccrine sweating, which may be compromised in MS patients (89). Precooling allows heat-sensitive individuals with MS to perform exercise with greater physical comfort and fewer side effects (86). The heat load induced via increases in metabolism during exercise appears to be reduced most effectively by cooling the greatest body mass while minimizing thermogenic responses (i.e., shivering) (85). This cooling (or temperature-blunting effect) can last for several hours, depending on the intensity of the activities performed by the individual with MS.

Investigations have examined the use of cooling garments (microclimate cooling) to combat heat-induced worsening of symptoms in MS patients during daily activities or during exercise (4, 9, 20, 37, 38, 40, 49, 68). Typically these garments come in two designs based on heat exchange properties. Active heat exchange garments are cooled by circulating liquid throughout the garment through a tubing network (21, 82). Passive heat exchange garments have ice or gel packs that are inserted into the garment to provide the cooling effect (75). Cooling garments have demonstrated improvements in neurological function (motor performance and visual acuity) as well as perceived subjective benefits (feeling less fatigued) in thermally sensitive MS patients (4, 9, 20, 37, 40, 68). A number of factors influence the ability of these garments to provide effective cooling: *1*) garment fit, *2*) location of cooling elements within the garment, *3*) cooling temperature and whether the cooling process is continuous or intermittent, *4*) body size and shape, and *5*) control and regulation of skin blood flow of the skin being cooled (8, 54, 75, 91). Although microclimate cooling has been shown to be effective in reducing heat stress in MS, some caution must be considered because cooling garments may increase metabolic rate and arterial blood pressure, and decrease mechanical efficiency for patients with

disabilities during the performance of physical work due to cooling equipment weight or restrictions in joint mobility. The cost of these garments also my limit accessibility and availability to some individuals with MS.

In addition to the previously described precooling and cooling strategies, pharmacological strategies have also been employed to preserve axonal conduction in MS patients. Pharmaceuticals, such as potassium channel blockers, have been prescribed by physicians to treat heat sensitivity in MS patients. 4-Aminopyridine, a potassium channel blocker, has been shown to increase the conduction of action potentials in demyelinated axons by inhibiting potassium channels (34). This drug has recently been shown to improve walking speed in MS patients (25). The Federal Drug Administration recently granted approval for the use of this drug in all forms of MS to improve or preserve mobility. Anecdotal evidence suggests this drug may limit the worsening of MS symptoms during heat exposure or exercise. Investigations are currently under way to determine if pharmaceutical interventions, such as 4-aminopyridine, can protectively modulate axonal channels and improve neural function in individuals with MS during thermal stress. Preliminary pilot data (unpublished observation) indicate that 4-aminopyridine provides some resistance to temperature-induced slowing in horizontal eye movements previously observed in MS patients with internuclear ophthalmoparesis (15).

Perspectives and Summary

Heat stress presents a significant problem to the individual with MS. Despite recent insights into thermoregulatory dysfunction in MS, many questions remain unanswered. Disease involvement in thermoregulatory centers within the CNS, specifically the hypothalamus, likely impairs thermoregulatory function. Quantification of MS involvement in gray matter in the CNS, specifically within the thermoregulatory centers of the hypothalamus, is needed and now may be possible with continuing advances in magnetic resonance imaging techniques. Recent evidence indicates that increased temperature alters conduction characteristics within the CNS of MS patients. It is unclear whether impaired conduction within the CNS with MS alters the processing of afferent information or whether there is an alteration in neural communication between higher brain centers. Progress in functional imaging techniques has the potential to provide information on activation patterns within thermoregulatory centers of the CNS in MS. Further research is also need to determine if the homeostatic control of body temperature is impaired in MS, resulting in individuals with MS operating in lower ranges of core temperature compared with controls. Evidence indicates that thermoeffector responses are impaired in MS. Heat dissipation mechanisms, specifically sweat function, in individuals with MS are reduced compared with healthy controls. It is unclear whether these impairments are related to impairments in neural control or peripheral alterations due to altered neural innervation or a combination of both. Hydration status is another area that warrants further investigation in MS. Patients often voluntarily restrict fluid intake to ease MS related bladder problems (i.e., bladder urgency, frequency of urination, bladder leakage), which could lead to decreases in plasma volume impacting thermoregulatory mechanisms, specifically sweating. Cooling techniques, including precooling, have been shown to be ef-
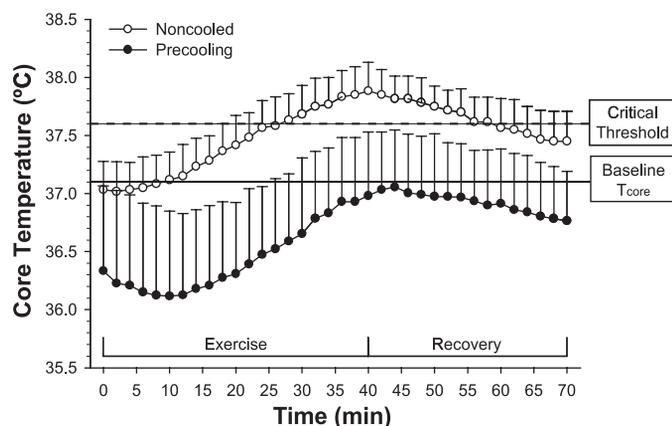
Fig. 4. Core body temperatures responses during 30 min of aerobic exercise and subsequent recovery following a noncooled trial (open circles) and a precooled trial (closed circles). Core body temperature during the precooled trial remained below baseline values during exercise and recovery whereas core temperature during the noncooled trial exceeded a critical threshold (0.5°C) for potential increases in symptom worsening. Data are expressed as means ± SD. Modified from White et al. (86) with permission from Sage Publication Ltd., UK.

fective in minimizing the consequences of heat stress in MS patients. Advances in pharmacological therapies have demonstrated potential in limiting symptom worsening during heat exposure and warrant further investigation.

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