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Autonomic Dysfunction in Multiple Sclerosis: Implications for Exercise

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Abstract

Multiple sclerosis (MS), a progressive neurological disease, can result in autonomic dysfunction. Impairments in the autonomic control of cardiovascular and thermoregulatory function during exercise have been observed in MS. Attenuated elevations in blood pressure during exercise in MS patients can negatively impact blood flow to skeletal muscle. Diminished sweating during exercise may impair heat dissipation likely limiting the exercise intensity that can be performed before detrimental core temperatures are reached. Further understanding the physiologic mechanisms of autonomic dysfunction during exercise in MS may lead to the development of novel therapeutic strategies targeted at improving quality of life in individuals with this disease.

Keywords

demyelination; cardiovascular; blood pressure; thermoregulation; sweat; sympathetic nerve activity

Multiple sclerosis (MS) is a progressive immune-mediated disease of the central nervous system (CNS) resulting in the disruption or loss of axonal myelin. Throughout the developed world, MS is the most common cause of neurological disability in young adults, affecting more than 2.3 million people worldwide (30). MS is characterized by a myriad of signs and symptoms that can lead to diminished functional capacity, increased disability, and reduced quality of life.

MS involves autoimmune injury cascades resulting in the disruption or loss of axonal myelin, formation of scar tissue (sclerosis), and ultimately axonal loss (12). Despite more myelin being present in white matter, growing evidence indicates that grey matter

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involvement occurs early in the disease process and may be a better predictor of disability in MS patients compared to white matter demyelination (15, 16). Grey matter areas of the brain such as the hypothalamus, medulla, and brainstem are susceptible to demyelination thereby resulting in impaired control of autonomic and endocrine function in MS (2, 20).

The assessment and understanding of autonomic function in MS patients has been problematic due to the variability of clinical symptoms and the heterogeneity in the clinical course of the disease over time. In addition, isolating and interpreting the mechanisms responsible for autonomic dysfunction due to MS can be difficult as it may involve sensory impairments, altered neural integration within the CNS, impaired effector responses, or combinations of all of these factors. Despite these difficulties, it is clear that autonomic dysfunction involving the genito-urinary, gastrointestinal, cardiovascular, and thermoregulatory systems are commonly observed and described in MS (18). Dysfunction may increase with disease progression and increased clinical disability (9). Of these, cardiovascular and thermoregulatory autonomic dysfunctions in MS have considerable potential to adversely affect exercise. This review will focus on autonomic impairments in the control of cardiovascular and thermoregulatory function and the impact of these impairments on the ability of relapsing-remitting MS patients to tolerate exercise and physical activity. The scope of this review is limited to relapsing-remitting MS, the most commonly diagnosed subtype of MS (24, 25), as the majority of experimental evidence on MS and exercise is performed on these patients. The importance of this topic is emphasized by the repeated demonstration of the significant benefits of regular physical activity/exercise to MS patients in terms of an improved sense of well being, reduced fatigue, and greater safety during walking (23, 28).

Autonomic Impairments of Cardiovascular Function

The prevalence of impairments in the autonomic control of cardiovascular function in MS patients from the previous studies has ranged from 7% to 60% when using standard tests, including the Valsalva maneuver, hand grip test, deep breathing, and standing test (1, 9–11, 14, 29, 35, 41–43, 47). Keller et al. recently reported that direct measures of spontaneous, resting muscle sympathetic nerve activity (MSNA) were reduced in MS patients compared to healthy individuals (22). Moreover, reduced plasma concentrations of norepinephrine mirrored the findings of reduced MSNA in MS (22). Forearm blood flow was also lower in MS patients compared to healthy controls at baseline conditions and during a reactive hyperemia challenge following cuff occlusion (39). Taken together, these observations suggest an altered control of the skeletal muscle circulation. It also suggests impairments may be occurring not only within the central nervous system (i.e., sympathetic outflow) but in combination with impaired responsiveness of mechano- and chemoreceptors within the muscle, which are also important for blood flow and blood pressure regulation (21, 48). Despite these studies investigating autonomic control of cardiovascular function in MS, most are descriptive in nature with a variety of methodologies, which may account for the large variation in the reported prevalence of autonomic/cardiovascular dysfunction with MS.

The implications of cardiovascular autonomic dysfunction in MS on exercise are even more convoluted, as few exercise studies have been performed to date. Several studies have

examined exercise pressor responses during isometric exercise. Blunted heart rate (HR) responses to isometric handgrip exercise have been reported, possibly due to specific lesions within higher brain centers thereby affecting central autonomic interconnections (i.e., central command) (44). Similarly, MS patients were incapable of increasing arterial pressure during handgrip exercise (36). However, diverging from Thomaides et al., observed HR responses to isometric handgrip exercise were similar between MS patients and healthy controls (36). Ng and colleagues also reported blunted arterial pressure responses to isometric leg exercise but no differences in HR responses compared to healthy controls (33). Ng et al. suggest that these observed responses are due to a diminished afferent signal from the muscle and not a generalized cardiovascular autonomic impairment (33). Collectively, these studies further illustrate the complex interaction between peripheral and central factors of cardiovascular impairments with this disease.

Only a few studies assessing cardiovascular responses to dynamic exercise in MS patients have been reported. Senaratne and colleagues reported attenuated elevations in HR and systolic blood pressure in MS patients during graded arm ergometry (intensity range: 30–110 Watts) (42). Similarly, Cohen et al. found blunted HR and systolic blood pressure responses to graded cycling (intensity range: 25 Watts with 10 Watt increments every 3 min) in MS patients compared to healthy controls (4).

Despite the potential exercise and health-related concerns, understanding of the exact mechanisms responsible for reduced arterial blood pressure control and the physiological consequences of these impairments to exercise in MS remains incomplete. Notwithstanding, attenuated elevations in arterial pressure during isometric and dynamic exercise seem to be consistent across studies. These abnormal pressor responses could impact exercise performance by altering perfusion pressure which in turn leads to insufficient blood flow to working skeletal muscle to meet metabolic demand. Although these cardiovascular abnormalities are disadvantageous, the benefits of aerobic exercise for individuals with MS heavily outweigh these adversities (37). Health professionals should prescribe exercise for MS patients at lower intensities so as to account for diseased-imposed limitations within the cardiovascular system. While the progression of aerobic exercise may need to be adjusted in smaller intervals and over longer periods, chronic improvements in aerobic fitness and quality of life indicators can still be observed with aerobic exercise training in MS patients (23, 28, 37, 38).

Autonomic Impairments of Thermoregulatory Function

The majority of MS patients experience transient and temporary worsening of clinical signs and neurological symptoms upon exposure to a hot (and often humid) environment and/or exercise, termed Uhthoff’s phenomenon (8, 13, 45). It is estimated that 60 to 80% of the MS population experience Uhthoff’s phenomenon as a result of elevated body temperature (17, 26, 31, 32). The precise mechanisms responsible are not completely understood and the current state-of-knowledge is reviewed in detail elsewhere (8, 13).

Complicating this heat sensitivity, thermoregulatory research performed on MS patients to date suggests that sudomotor function (i.e., sweating) may be suppressed relative to healthy

controls (3, 34, 40, 46), indicating heat storage (and changes in core temperature) may be greater at given rate of metabolic heat production. Davis et al. (7) observed diminished sweat function in MS patients caused by reduced sweat output per gland, rather than reduced gland recruitment during peripheral administration of a cholinergic agonist (pilocarpine) to eccrine sweat glands. Davis et al. documented significantly lower sweating responses in MS patients when internal temperature was increased ~1.0 °C by passive heating (6). These passive heating responses were not affected by local heating but rather were due to reflex-induced neural modulation in response to changing internal body temperature (6). To discount deconditioning as a potential factor for diminished sweating, Davis et al. (7) aerobically trained MS patients for 15 weeks. No improvements in pilocarpine-induced sweat function were subsequently observed in MS patients suggesting that MS likely impairs autonomic control of thermoregulatory effector responses as the thermoregulatory adaptations to exercise training typically observed in healthy individuals were absent in MS patients (7). Taken together, diminished sweat function could indicate autonomic impairments in neural control of sudomotor pathways and/or neural-induced peripheral changes in eccrine sweat glands (i.e., gland atrophy) (2, 46). Impaired sweating appears to occur more frequently in MS patients with more severe or progressive cases of disease (3). However, these studies are limited to observing MS patients at baseline conditions and/or during a passive heat stress.

Although heat strain intensifies MS symptoms, physical activity can still be theoretically prescribed and performed if the intensity is sufficiently low to maintain body temperature within acceptable limits. Change in body temperature of an individual of a given mass is greatly determined by the cumulative difference between internal metabolic heat production and net heat dissipation to the surrounding environment (5). The exercise intensity that can be performed before detrimental core temperatures are reached in an MS patient is dependent on the person’s ability to shed heat at the skin surface via the evaporation of sweat secreted onto the skin surface. It follows that any decrements in sudomotor control secondary to the demyelinating effects of MS will alter the level of physical activity that can be performed under particular environmental conditions. In efforts to counteract physiologically uncompensable environments, precooling and cooling strategies can be employed to reduce or control MS related symptoms (reviewed in detail by Davis and colleagues) (8).

Little has been done to examine thermoregulatory function in MS patients during exercise. Recently, a delay in the onset of sweating and a diminished thermosensitivity of sweat rate for a given subsequent displacement in esophageal temperature was observed in a preliminary study comparing thermoregulatory function between MS patients and mass-matched healthy controls during recumbent cycling exercise at a fixed rate of metabolic heat production (340 Watts) (19). Furthermore, the change in rectal temperature following 60 minutes of cycling was almost doubled in the MS patients compared to the healthy control group. To our knowledge, this is the first study to quantify and explain mechanistically the thermoregulatory dysfunction experienced by MS patients during exercise (19). Further research is warranted to give rise to safe yet effective exercise parameters and strategies for individuals living with MS.

Conclusion

Compounding evidence now indicates that regular exercise without a critical attendant heat strain is beneficial to individuals with MS, and should be incorporated into their overall disease management plan (23, 28, 38). However, it is clear that MS patients typically engage in significantly less physical activity relative to their healthy counterparts (27, 28). Unclear is how the sequela of MS in the form of cardiovascular and thermoregulatory autonomic dysfunction impacts exercise tolerance and capacity and more importantly, what exact physiological mechanisms are contributing to these dysfunctions. If these mechanisms can be identified, appropriate therapeutic and/or pharmacological interventions can be developed to reduce their impact on exercise and heat tolerance, ultimately increasing not only health but also quality of life of MS patients.

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