Autonomic Neuroscience: Basic and Clinical 188 (2015) 82–85

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Review

Autonomic dysfunction in multiple sclerosis: Implications for exercise

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ARTICLE INFO

Article history:
Received 30 May 2014
Received in revised form 11 September 2014
Accepted 13 October 2014

Keywords:
Demyelination
Cardiovascular
Blood pressure
Thermoregulation
Sweat
Sympathetic nerve activity

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.

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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 (National Multiple Sclerosis Society). 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 (Frohman et al., 2006). Despite more myelin being present in white matter, growing evidence indicates that gray matter involvement occurs early in the disease process and may be a better predictor of disability in MS patients compared to white matter demyelination (Geurts and Barkhof, 2008; Geurts et al., 2012). Gray 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 (Andersen and Nordenbo, 1997; Huitinga et al., 2004).

The assessment and understanding of autonomic function in MS patients have 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 is commonly observed and described in MS (Haensch and Jorg, 2006). Dysfunction may increase with disease progression and

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http://dx.doi.org/10.1016/j.autneu.2014.10.017
1566-0702/

increased clinical disability (Flachenecker et al., 2001). 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 (Lublin and Reingold, 1996; Lublin et al., 2014), 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 (Latimer-Cheung et al., 2013; Motl and Pilutti, 2012).

1. 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 (Acevedo et al., 2000; Flachenecker et al., 2001, 2003, 1999; Frontoni et al., 1996; Nasseri et al., 1998; Pentland and Ewing, 1987; Sanya et al., 2005; Senaratne et al., 1984; Sterman et al., 1985; Vita et al., 1993). 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 (Keller et al., 2014). Moreover, reduced plasma concentrations of norepinephrine mirrored the findings of reduced MSNA in MS (Keller et al., 2014). 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 (Ranadive et al., 2012). Taken together, these observations suggest an altered control of the skeletal muscle circulation. It also suggests that 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 (Joyner et al., 2010; Wallin and Charkoudian, 2007). 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) (Thomaides et al., 1993). Similarly, MS patients were incapable of increasing arterial pressure during handgrip exercise (Pepin et al., 1996). However, diverging from Thomaides et al., observed HR responses to isometric handgrip exercise were similar between MS patients and healthy controls (Pepin et al., 1996). Ng and colleagues also reported blunted arterial pressure responses to isometric leg exercise but no differences in HR responses compared to healthy controls (Ng et al., 2000). 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 (Ng et al., 2000). 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 W) (Senaratne et al., 1984). Similarly, Cohen et al. found blunted HR and systolic blood pressure responses to graded cycling (intensity range: 25 W with 10 W increments every 3 min) in MS patients compared to healthy controls (Cohen et al., 1989).

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 (Petajan et al., 1996). 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 (Latimer-Cheung et al., 2013; Motl and Pilutti, 2012; Petajan et al., 1996; Petajan and White, 1999).

2. 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 (Davis et al., 2010b; Frohman et al., 2013; Uhthoff, 1889). It is estimated that 60 to 80% of the MS population experience Uhthoff's phenomenon as a result of elevated body temperature (Guthrie, 1951; Malhotra and Goren, 1981; Nelson et al., 1958; Nelson and Mc, 1959). The precise mechanisms responsible are not completely understood and the current state-of-knowledge is reviewed in detail elsewhere (Davis et al., 2010b; Frohman et al., 2013).

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 (Cartlidge, 1972; Noronha et al., 1968; Saari et al., 2009; Vas, 1969), indicating heat storage (and changes in core temperature) may be greater at a given rate of metabolic heat production. Davis et al. (2005) 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 (Davis et al., 2010a). 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 (Davis et al., 2010a). To discount deconditioning as a potential factor for diminished sweating, Davis et al. (2005) 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 (Davis et al., 2005). 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) (Andersen and Nordenbo, 1997; Vas, 1969). Impaired sweating appears to occur more frequently in MS patients with more severe or progressive cases of the disease (Cartlidge, 1972). However, these studies are limited to observing MS patients at baseline conditions and/or during a passive heat stress.