# Thermal dysregulation in patients with multiple sclerosis during SARS-CoV-2 infection. The potential therapeutic role of exercise

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**Highlights:**

- Thermoregulation is a necessary component of daily life.
- COVID-19 causes thermal dysregulation and increases core body temperature.
- Individuals with multiple sclerosis (MS) are sensitive to increases in core body temperature.
- Being physically active triggers adaptations that alleviate COVID-19-induced thermal dysregulation.
- Engaging in regular physical activity before and after infection with COVID-19 attenuates worsening clinical signs and reduces recovery time in patients with MS.

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**Abstract**

Thermoregulation is a homeostatic mechanism that is disrupted in some neurological diseases. Patients with multiple sclerosis (MS) are susceptible to increases in body temperature, especially with more severe neurological signs. This condition can become intolerable when these patients suffer febrile infections such as coronavirus disease-2019 (COVID-19). We review the mechanisms of hyperthermia in patients with MS, and they may encounter when infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Finally, the thermoregulatory role and relevant adaptation to regular physical exercise are summarized.

**Keywords**

Multiple sclerosis; exercise; thermoregulation; sweat gland; SARS-CoV-2; ANS, Autonomic nervous system; APN, Adiponectin; CNS, Central nervous system; COVID-19, Coronavirus disease-2019; EDHF, Endothelial-derived hyperpolarizing factor; eNOS, Endothelial nitric oxide synthase; MS, Multiple sclerosis; NLRP3, NLR family pyrin domain containing 3; NO, Nitric oxide; PACAP, Pituitary adenylate cyclase-activating polypeptide; PAMPs, Pathogen-associated molecular patterns; PGs, Prostaglandins; $PGE_2$, Prostaglandin $E_2$; ROS, Reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNS, Sympathetic nervous system; TRPV-1, Transient receptor potential vanilloid type 1; VDP, Vascular-dilating prostanoids; VEGF, Vascular endothelial growth factor; VIP, Vasoactive intestinal peptide

## 1. Introduction

Multiple sclerosis (MS) is a neurodegenerative disease characterized by lesions of the central nervous system (CNS). A unique feature of this autoimmune disease is the high prevalence (60–80%) of temperature sensitivity, where neurological signs are exacerbated by increases in environmental or internal body temperatures. The regulation of a near constant body temperature within a physiological range is required for survival and daily function (Corbett et al., 2014). Body temperature is composed of central and skin temperature (Gisolfi et al., 2000; Lim et al.,

2008; Lim and Suzuki, 2017). Core temperature is centrally regulated by the brain in response to changes in thermal balance (Gisolfi et al., 2000; Lim, 2020). Venous blood temperature and afferent signals from thermo-sensitive nerves on the body surface act to regulate autonomic nervous and behavioral responses to regulate body temperature (Lim et al., 2008). The control of temperature in the body results from a balance between heat gain and its dissipation (Lim, 2020). Thermoregulation in humans is accomplished by several independent loops of the thermoregulatory reflex. Peripheral receptors are activated by increases in skin and core temperatures, and activate afferent nerves to signal the preoptic anterior hypothalamus as the integrating center. After integrating the thermal-afferent information, increased efferent nerve outflows lead to activating the thermal-effector responses that result in sweating and cutaneous vasodilation consequent to releasing of acetylcholine and other co-transmitters such as vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), vascular-dilating prostanoids (VDP), substance P (SP), and channels of transient receptor potential vanilloid type 1 (TRPV-1) (Francisco and Minson, 2018; Gagnon et al., 2016; Taylor, 2011; White et al., 1996). Disturbances of this thermoregulatory reflex occurs in some diseases such as MS, a disease of demyelination, which affects neural conduction.

Thermal fluctuations impact neural conduction (Morrison and Blessing, 2011). Inactivity reduces the reactivity of cutaneous small-vessels, and increases core temperature (Wang, 2005). This could underlie the high sensitivity of patients with MS to increases in core body temperature induced by exogenous agents such as viral infections. Individuals infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also experience increased core body temperatures, which can exacerbate temperature dysregulation in patients with preexisting dysregulation of body temperature. We review temperature dysregulation in patients with MS and the added burden of the coronavirus disease-19 (COVID-19) pandemic. In addition, we also discuss the adaptions produced by regular physical exercise as an adjunct procedure to mitigate the effects of heat in patients with MS infected the SARS-CoV-2.

**2. Thermal dysregulation in MS patients as a challenge during SARS-CoV-2 infection**

MS is the primary cause of neuronal dysfunction in juveniles (Edmonds et al., 2010). The autonomic nervous system (ANS) is severely impacted in individuals with MS (Gunal et al., 2002), where dysfunction of sympathetic and parasympathetic nerves is associated with a range of diverse clinical disabilities (Flachenecker et al., 2001; Habek, 2019). Autonomic dysfunction

in MS is related to lesions in the periventricular region of the fourth ventricle of the brainstem and medulla (Adamec and Habek, 2013). Autonomic dysfunction results from both demyelination and also axonal loss (de Seze et al., 2001), affecting cardiovascular (66% of patients) (Acevedo et al., 2000; Mincu et al., 2015), bladder (97% of patients) (Haensch and Jörg, 2006), sexual function (80% of patients) (Tepavcevic et al., 2008), bowel (43% of patients) (Hinds et al., 1990), sleep (50% of patients) (Bamer et al., 2008), heat sensitivity (60-90% of patients) (Gallup et al., 2010) and also altered motor symptoms (e.g., fatigue) (thermoregulation). Hypothalamic lesions can result in both hyperthermia and hypothermia (Linker et al., 2006; White et al., 1996). Increasing core body temperature occurs commonly in patients with MS and can be due to interruptions in central sudomotor pathways which originate from the preoptic hypothalamic area and descend to the intermediolateral of the spinal cord to exit from the central nervous system (CNS) to innervate sweat glands that can lower core temperature (Adamec and Habek, 2013; Saari et al., 2009). Impairment of this pathway worsens neurological signs and symptoms and in severe cases can increase heat sensitivity or Uhthoff phenomenon/syndrome, which describes a transient worsening of neurological symptoms (caused by hot weather, exercise, fever, being in a heated environment etc.) due to demyelination in MS (Jain et al., 2020). Up to 60 to 80% of MS patients experience this phenomenon that can be triggered by increases in core temperature by as little as 0.5˚C, resulting in transient symptoms such as visual blurring (Cianfrone et al., 2006; Filingeri et al., 2017; Jain et al., 2020; Syndulko et al., 1996; Wilson et al., 2010). The first report on visual blurring with exercise as a heat stressor was described in 1890 by Uhthoff, who attributed it to increases in core body temperature, leading to the avoidance of exercise by patients with MS (Baker, 2002; Frohman et al., 2013).

Thermal sensitivity is usually measured in patients with MS by responses to heat (e.g., using hot water immersion, heat lamp, and heat cabinet) and evaluating emerging or worsening neurological signs (Leavitt et al., 2014; Nelson et al., 1958; Nelson and McDowell, 1959). Initial studies on healthy individuals, people with neurological disorders and patients with MS reported that two patients with MS died after exposure to increased body temperatures of up to 40 ˚C for 8-10 hours; patients with MS experienced motor weakness, amblyopia, and visual deficits following a heat stress. Such sensitivity in patients with MS even occurred after exposure one limb to temperature increase of up to ~ 0.5˚C (Guthrie, 1950; Guthrie, 1951). A later study of responses to a heat stress (55-60˚C) in patients with MS reported worsening of signs in 75%

patients within 10-15 min (EDMUND and FOG, 1955). Another study indicated that clinical signs appeared in patients with MS after 8 min when body temperatures were increased by 0.8˚ C; clinical signs peaked when body temperature was increased by 1.7˚C for 28 min (Nelson et al., 1958).

Some studies also suggest that increased core body temperature in patients with MS could result from lowered sweating rates as well as delayed sweat initiation (Krupp et al., 2007; Petajan and White, 1999), or having a higher sweat threshold (Baker, 2002; Huang et al., 2015; Racosta et al., 2015). In addition, the reduction in sweating function in MS patients is largely due to decreased sweat output in individual sweat glands rather than to reduced gland recruitment (Davis et al., 2010a), and that 15 weeks of aerobic endurance was unable to improve sweat function in patients with MS. Thus, heat sensitivity is a characteristic feature of MS (Davis et al., 2005).

Regardless of being a frequent complaint in patients with MS, our understanding of how increases or decreases in body temperature contribute to worsening of MS symptoms is incomplete. However, as depicted in ***Figure 1***, the most likely mechanisms underlying heat sensitivity and the exacerbation of the symptoms of MS can be summarized as follow:

A) Demyelinated axons in brain lesions and peripheral neurons overexpress voltage-gated $Na^+$ ($Na_v$) channels, particularly α-subunits, throughout their length (Smith, 2007; Tartas et al., 2004). There have been generally revealed 9 isoforms of this type of $Na_v$ channels ($Na_v1.1$ to 1.9). The isoforms of $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, and $Na_v1.6$ extremely expressed in CNS (Egri and Ruben, 2012). These channels influence enormous characteristics of neurons including refractory phase and excitability of neurons. The contribution of these channels in neuronal electrogenesis is formed based on their different spatial distribution within the axon membrane, with high density in the axon membrane at the node of Ranvier and much lower density in other areas beneath myelin including paranodal and intermodal axon membrane (Peles and Salzer, 2000; Waxman, 1998). Sodium channels illustrate a dynamic changes either in normal CNS (during development) or in pathological CNS. It has been reported that MS patients and its animal model, experimental autoimmune encephalomyelitis (EAE), experience a plasticity in $Na_v$ channels in both expression and distribution levels. Notably, $Na_v1.2$ and 1.6 are the most isoforms undergoing increased expression and also they extended to the paranodal and

juxtaparanodal areas (Craner et al., 2003; Craner et al., 2004b). Increased $Na_v$ channels is associated with some changes in impulse conductance and hyperexcitibility and exacerbating the clinical signs of these patients is partly due to a persistent sodium current which may accompany neural damage and loss of axons that transfer information on central temperature to hypothalamus. Increased intracellular $Na^+$ will cause $Ca^{2+}$ dysregulation, including by acting on $Na^+/Ca^{2+}$ exchange. Intracellular accrual of $Ca^{2+}$ initiates neural and axon damages through activating some catabolic enzymes, including proteases and calpains (Agrawal and Fehlings, 1996; Correale et al., 2019; Craner et al., 2004a; Craner et al., 2004b; Stys et al., 1993; Stys et al., 1992). Upon losing the central and peripheral neurons, thus, MS patients in progressive phase of disease do not have an accurate perception of how extent their central body temperature has been increased.

B) Roughly 20% of hypothalamic neurons are stratified as a thermal-sensitive neurons with high rates of action potential in proportional with other thermal-nonsensetive ones (Wechselberger et al., 2006). These neurons not only respond to the temperature of hypothalamus but receive afferent synaptic inputs from skin and spinal thermorecptors; hence, they integrate the central and peripheral temperatures. Thermal sensitivity of these hypothalamic neurons partly results from some selective ionic channels (Boulant and Hardy, 1974; Wechselberger et al., 2006). Normal function of neurons depends on regularly fire action potentials and maintenance resting membrane potentials. In this regard, potassium channels including two-pore domain $K^+$ (K2P) channels contribute to the steady outward leak of $K^+$ ions and consequent restoring of the rate of action potential (Braun, 2012). Humans express 14 K2P channels which have been categorized into 5 subgroups (Patel and Honoré, 2001). These channels play a leading role in establishing resting membrane potential, regulating potential duration and modulating the response to synaptic inputs (Griffin et al., 1996; Patel and Honoré, 2001; Rush and Rinzel, 1995). Besides, the most majority of potassium channels extensively express in human brain (Maingret et al., 2000; Patel and Honoré, 2001). A scrutiny on every subunit of K2P channels is beyond the scope of this review. Although there is not conclusive document about these channels expression in axons extruded in hypothalamic area and hypothalamic neurons in MS patients, their expression is main factor impacting the thermal sensitivity of neurons. These channels are not voltage-gated, since the absence of

canonical voltage sensor domain (Braun, 2012; Medhurst et al., 2001; Wechselberger et al., 2006). In this context, their activity is influenced by physical and chemical stimuli, including mechanical and heat stresses (Braun, 2012). Peripheral and central hyperthermia activate K2P channels, causing the outward flow of potassium ions from neurons and resulting in neuronal hyperpolarization and decreased action potential propagation (Griffin and Boulant, 1995; Wechselberger et al., 2006). Notably, the higher expression of K2P channels on thermal-sensitive neurons, the higher potassium leak current and the lower firing rate of action potentials. In accordance with their extensive expression in brain, potassium channels may be selective candidate in increased thermal sensitivity. In any case, the expression changes of potassium channels in afferent peripheral and central neurons and their role in altering thermal sensitivity of MS patients should be precisely investigated by future studies.

C) Hypothalamic lesion-induced impairments in sympathetic outflows and the destruction of sudomotor pathways reduces sweating and consequently increases body temperature (Haensch and Jörg, 2006; Huang et al., 2015; Keller et al., 2014).

D) There is decreased sweat output per gland (Davis et al., 2005).

E) The reduced current available to excite node of Ranvier results in a blockade in neuronal conduction (Allen, 2018; Davis et al., 2018; Davis et al., 2010b).

F) Other factors that could reduce conduction speed in demyelinated fibers include vasoconstriction and humoral factors (Syndulko et al., 1996). Fatigue, which is associated with heat stress and which occurs in approximately 70% of individuals with MS individuals (Krupp, 2003; Krupp et al., 2007; Marino, 2009; Martin et al., 2005; Nybo and Nielsen, 2001), can result from demyelinated lesions that lower central motor conduction and cortical excitability (Humm et al., 2004; Petajan and White, 2000; Sheean et al., 1997; White et al., 2008). There is evidence that patients with advanced MS pathology likely have more failures in impulse conduction (Smith and McDonald, 1999).

The ability to sense changes in skin temperature drives behavioral responses to heat stress (e.g., decreased physical work, removing clothes, seeking shade, etc.) and can also influence autonomic thermoregulation (Davis et al., 2018; Davis et al., 2010b; Huang et al., 2015; Huang et al., 2014). Studies by Filingere and colleagues (Davis et al., 2005) that used heat sensitivity of skin afferents using exercise as a heat stressor, and also by exposing them to a cold environment,

indicated that cold sensitivity is decreased in patients with MS, suggesting that MS pathophysiology independently modulates afferent thermosensory function. Reduced cold-induced conduction speed in nerve fibers is greatest in A fibers, followed by B fibers and less so in C fibers (Syndulko et al., 1996). This divergence in susceptibility to cold block may be related to nerve characteristics such as myelination, diameter, and threshold characteristics. This is supported by findings that nerve fibers, especially A fibers which have lower thresholds, faster conduction, greater myelination and diameters, have greater sensitivity to cold block (Douglas and Malcolm, 1955; Todd, 2002). Several studies suggest that contrary to expectations, the conduction velocity in sensory nerve fibers is increased by higher limb temperatures (Franssen et al., 1999; Franssen and Wieneke, 1994; Tavee, 2019).

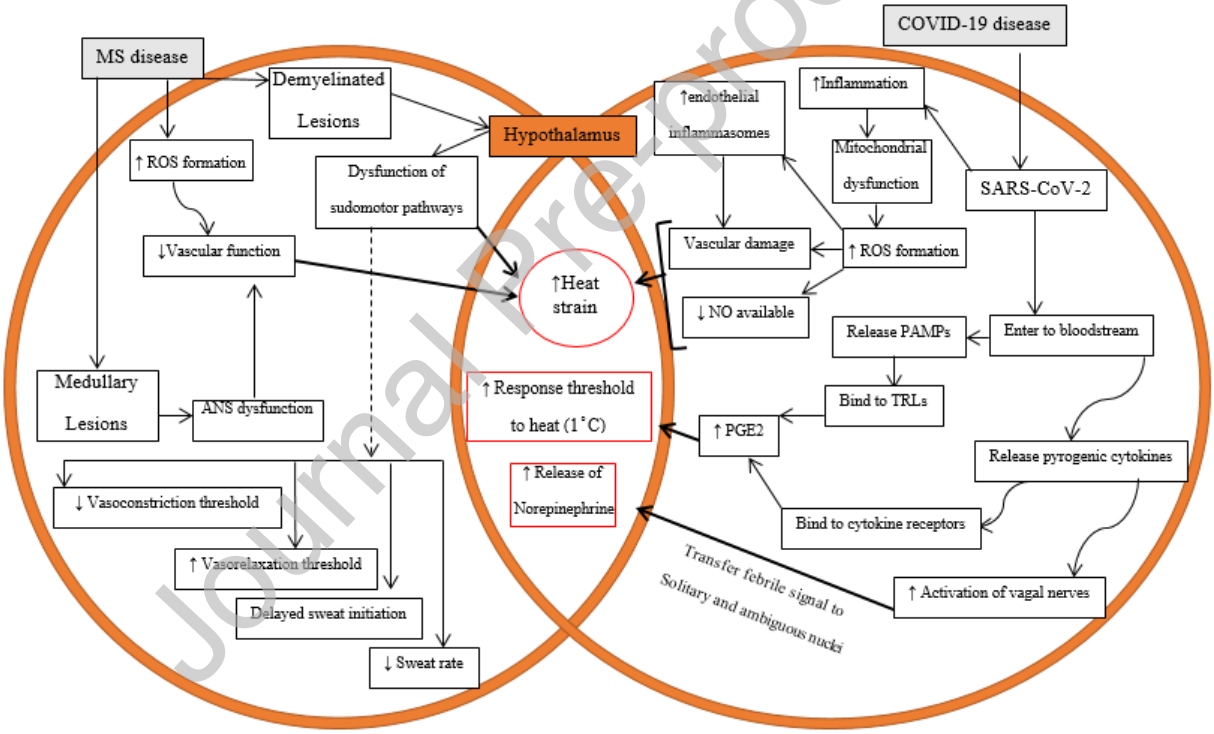


**Figure. 1.** Schematic representation of dysfunctional pathways of thermoregulation in individuals with MS disease and the exacerbating role of COVID-19 in increasing heat strain. MS, multiple sclerosis; COVID-19, coronavirus disease-2019; ANS, autonomic nervous system; ROS, reactive oxygen species; NO, nitric oxide; PAMPs, pathogen-associated molecular patterns; TLRs, toll-like receptors; $PGE_2$, prostaglandin $E_2$.

Body temperature fluctuations in patients with MS with infectious conditions, such as during the COVID-19 pandemic, could be exacerbated since there is a limited ability to mount counteracting febrile responses in these patients (Davis et al., 2010b). Although the majority of COVID-19 patients are asymptomatic, many others manifest some serious clinical symptoms (Schneider et al., 2021; Wölfel et al., 2020). Fever occurs initially in more than 50% of patients affected with COVID-19 (Hui and Zumla, 2019; Islam et al., 2021; Qiu et al., 2020). Instant diagnosis of infection can prevent its transmission or to initiate countermeasures or successful confinements (Schneider et al., 2021). Although assessing fever may not be efficacious in all COVID-19 patients, it is however critical in individuals with pre-existing thermal dysregulation such as in patients with MS (Racke and Newsome, 2020; Schneider et al., 2021). Individuals with MS are at higher risk during the COVID-19 pandemic, as they often are treated with immunosuppressing drugs (IMDs) (Hughes et al., 2020; Loonstra et al., 2020; Louapre et al., 2020; Maghzi et al., 2020; Willis and Robertson, 2020). Importantly, both diseases (MS and COVID-19) share the ability to induce febrile responses characteristic of cytokine storms (Berger et al., 2020; García, 2020; Sorenson et al., 2017; Zheng et al., 2020).

Fever is part of defensive responses of multicellular organisms (host) to invasion of microorganisms such as viruses, including SARS-CoV-2 (Ogoina, 2011). The febrile response includes endocrine, neurological and immunological mechanisms (Dinarello and Gelfand, 2005; Mackowiak). SARS-CoV-2, as an exogenous pyrogen, can initiate the febrile responses through humoral and neuronal pathways (Ogoina, 2011). Upon entering the circulation, the virus then activates pathogen-associated molecular patterns (PAMPs) or pyrogenic cytokines [pro-inflammatory cytokines, namely, tumor necrosis factor-alpha (TNF-α), IL-1] (Conti et al., 2004; Jiang et al., 1999; Romanovsky et al., 2006; Steiner et al., 2006a; Turrin and Rivest, 2004). The circulatory microorganism's PAMPs and cytokines (released by host) activate toll-like receptors and cytokine receptors, respectively, on capillaries and also on the blood-brain barrier (BBB), leading to the release of prostaglandin $E_2$ ($PGE_2$) (Conti et al., 2004; Romanovsky et al., 2006; Steiner et al., 2006a; Turrin and Rivest, 2004). $PGE_2$ binds to EP2 receptors in the preoptic area to activate thermal neurons in the anterior hypothalamus and reset the thermal balance point to a higher set-point (Mackowiak; Romanovsky et al., 2006; Steiner et al., 2006a; Turrin and Rivest, 2004). It has been argued that the initial phase of the febrile response is dependent on $PGE_2$ synthetized in the liver and lungs prior to migrating to the brain, while the later phase of the

febrile response is due to centrally synthetized $PGE_2$ (Gross, 2006; Steiner et al., 2006b). Thus, exogenous pyrogens (such as SARS-CoV-2) are converted to endogenous pyrogens (PAMPs, cytokines) after entering the body. SARS-CoV-2 has a tropism for brainstem centers of the autonomic nervous system, where the virus serves to transfer a fever signal from peripheral nerves (such as the olfactory pathway) transfers to the hypothalamus, thalamus, and brainstem (Blatteis, 2007; Hopkins, 2007; Roth and De Souza, 2001; Xu et al., 2005). Much like fever produced by $PGE_2$, exogenous pyrogen such as SARS-CoV-2 can activate pyrogenic cytokines, which in turn activate the hepatic branch of the vagal nerve and transfer the febrile signal to nerves in solitary and ambiguous nuclei (Blatteis, 2007; Li et al., 2020; Matsuda et al., 2004; Roth and De Souza, 2001; Rummel et al., 2005). The signals from the solitary nucleus are delivered to preoptic and hypothalamic areas through the ventral noradrenergic bundle, resulting in norepinephrine release into these thermoregulatory areas (Blatteis, 2007; Roth and De Souza, 2001). Norepinephrine mediates the vagal pathway by raising core temperature. The resetting of the thermal balance point to a higher set-point through these two humoral and neuronal signals initiates a feedback loop leading to early vasoconstriction and some clinical and behavioral manifestations to maintain body temperature. When there is no longer a fever signal in the CNS, the set-point then returns normal levels to activate heat loss mechanisms such as sweating (Leggett, 2016; Mackowiak).

As discussed above, activation mechanisms to reduce core temperature are impaired in patients with MS. In addition, patients with MS have impairment in vascular function, likely related to reactive oxygen species (ROS)-induced oxidative stress (Dhalla et al., 2000; Fjeldstad et al., 2010; Ohl et al., 2016; Ranadive et al., 2012). Oxidative stress in patients with MS promotes viral replication (Li et al., 2017), while SARS-CoV-2 can impose a thermal burden through ROS production reduce nitric oxide (NO)-mediated vasodilation (Ghosh and Karin, 2002; Xu and Zou, 2009; Zhang, 2008). In addition, MS and COVID-19 leads to inflammation and increased mitochondria-derived ROS production (Alandijany et al., 2013). ROS upregulate endothelial inflammasomes [especially, NLR family pyrin domain containing 3 (NLRP3)] and their signals, including caspase-1 and IL-1β in endothelial cells, thus initiating vascular pathology (Long et al., 2020; Martinon et al., 2002).

High core temperature affects tissue metabolism, and can result in tissue necrosis, especially in neurons, and DNA unwinding (Nagashima et al., 2012). The prevalence of MS can be three

times higher than in men, and this can cause more severe symptoms because women have lower blood volumes, smaller heart sizes, a lower free fat mass, a higher percent of subcutaneous and whole fat, a higher body temperature threshold for dilating of cutaneous vessels, circadian changes in sex hormone levels that could lead to differences in body temperature regulation (MITCHELL et al., 1992).

**3. Exercise improves thermoregulation**

Homeothermic mechanisms cause intrinsic regulation of heat gain (metabolic production) and loss (sweat and evaporation) to maintain core body temperature set point (Gisolfi and Mora, 2016; Madden and Morrison, 2019; Zalewski et al., 2014). Fluctuation from set point of body temperature stimulates hypothalamus to restore core temperature through changes in behaviors and physiological responses induced by the ANS (Morrison and Blessing, 2011). Reductions and increases of core temperature trigger the activation of sympathetic efferent and cholinergic outflows, respectively. Adrenergic efferent release of norepinephrine to constrict cutaneous vessels, while cholinergic efferent secrete acetylcholine (Ach) to lower core temperature by vasodilation (Flouris and Schlader, 2015; Gordon et al., 2019; Morrison and Nakamura, 2019; Tansey and Johnson, 2015). Maintenance of core body temperature is critical for work output and prevents premature fatigue (Adams et al., 2019; Fehling et al., 2015; González-Alonso et al., 1999; Sawka et al., 2001). Physical exercise is a heat stressor that increases core body temperatures through increases in metabolism by exercising muscles (Nadel et al., 1987; Nadel et al., 1974). On the other hand, the adaptations induced by exercise training in cardiac output and stroke volume can mitigate this heat stress through facilitating heat transmission to the skin for cooling by evaporation, which is followed by a reduction in early fatigue (Geor and McCutcheon, 1998; Lim, 2020). Thus, improving body temperature regulation attenuates fatigue. Although physical exercise acts as a heat stressor, regular exposure to this stressor promotes adaptations that limit its detrimental effects (Périard et al., 2016). Although the increase in body temperature is probably a danger in MS patients, especially during or after an infection with corona virus, higher levels of heat stimulation are associated with greater adaptations in heat regulation (Périard et al., 2016). These adaptations to exercise training are akin to the adaptions induced by exposure to heat (Corbett et al., 2014; Nielsen et al., 1993; Weller et al., 2007). Importantly, the probable adaptations acquired from exercise training that help to maintain core body temperature within a narrow range consist of neurophysiological adaptations, including

cardiovascular, hematological, and hormonal changes, neural adaptations of the temperature set and thermoregulatory effectors, reduced production of metabolic heat by exercise, improved heat tolerance through the response to heat shock, and improved sweat economy (***Figure 2***) (Nadel, 1988; Nadel et al., 1980; Takeda and Okazaki, 2018; Werner, 1993; Yamauchi et al., 1997).

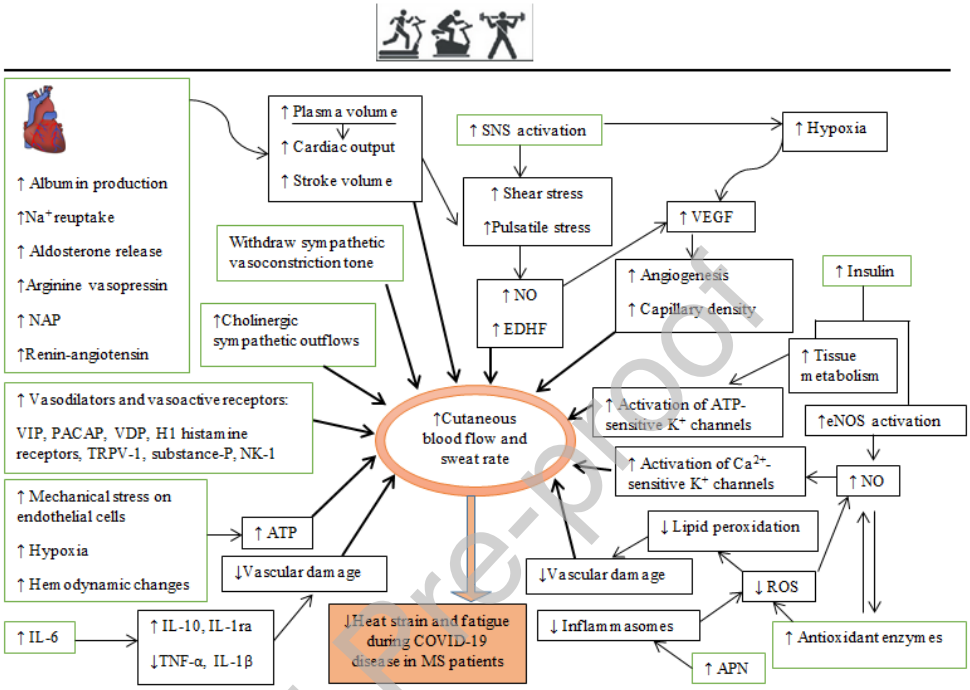


**Figure. 2**. Schematic diagram of physical exercise-induced adaptations in improving thermal management. The green rectangles represent the main adaptations induced directly by regular physical exercise that are associated with secondary adaptations (in black rectangles). The bold arrows show the main adaptations; oval circles indicate increased cutaneous blood flow resulting from vascular adaptations. $Na^+$, sodium; NAP, natriuretic atrial peptide; VIP, vasoactive intestinal peptide; PACAP, pituitary adenylate cyclase-activating polypeptide; VDP, vascular-dilating prostanoids; TRPV-1, transient receptor potential vanilloid type 1; NK-1, neurokinin-1; NO, nitric oxide; EDHF, endothelial-derived hyperpolarizing factor; VEGF, vascular endothelial growth factor; ROS, reactive oxygen species; APN, adiponectin.

The cardiovascular system regulates blood supply to exercising muscles to support their metabolism and also to the skin for dissipating the heat generated by exercising muscles (Geor and McCutcheon, 1996; Rowell, 2011). Autonomic processes such as skin vasodilation and sweat production are compensatory procedures to maintain body temperature at a normal level

(Kenny and McGinn, 2017; Nagashima et al., 2012). Exercise-induced hyperthermia impairs the function of ANS, which is measurable by heart rate variability and lasts > 80 min after the exercise session (Armstrong et al., 2012). Thus, other factors can restore body heat balance. The initial increase in skin blood flow during hyperthermia is primarily due to withdrawal of sympathetic vasoconstriction (McNamara et al., 2014; Wong, 2013). The 85-95% increase in cutaneous blood flow and increased sweating is mediated by cholinergic outflows from sympathetic nerves (Wong, 2013). Vasodilation and sweating is achieved by release of Ach from cholinergic terminals of sympathetic nerves and also by the co-release of other vasodilators (Bennett et al., 2003; Dean L. Kellogg et al., 2010; Johnson and Kellogg, 2010; Kellogg Jr et al., 1995; McCord et al., 2006; Wong, 2013; Wong et al., 2004). Vasoactive intestinal peptide (VIP) (Bennett et al., 2003; Dean L. Kellogg et al., 2010), pituitary adenylate cyclase-activating peptide (PACAP) (Rambotti et al., 2002; Wallengren, 1997; Warren et al., 1992), vitronectin-derived peptide (VDP) (McCord et al., 2006), histamine (Wong et al., 2004), and substance-P (Wong and Fieger, 2012; Wong and Minson, 2006) are co-released with Ach. These co-transmitters also increase the production of local NO (Kellogg Jr et al., 2012; Klede et al., 2003; McCord et al., 2006; Shibasaki et al., 2002; Wilkins et al., 2004; Wong, 2013; Wong et al., 2005; Wong et al., 2004). For instance, substance-P activates Neurokinin-1 (NK1) receptors to increase NO levels (Wong and Minson, 2006). However, substance-P also causes microvascular dilation by NO independent mechanisms by the degranulation of cutaneous mast cells, causing local increases in histamine levels (Huttunen et al., 1996). Increased cutaneous microvascular reactivity and function are positively related to $VO_2$max (Hodges et al., 2010; Middlebrooke et al., 2005; Roche et al., 2008; Tew et al., 2010).

Improvements in the thermoregulatory components produced by regular physical exercise, especially endurance/aerobic training, are related to increases in cardiac output and antioxidant enzyme levels (Tew et al., 2012; Tew et al., 2010), while increases in skin blood flow are due to increased plasma volume (Ikegawa et al., 2011). Aerobic exercise training for 6-10 days increases the plasma volume (Convertino, 1991; Costill et al., 1976; Fellmann, 1992; Williams et al., 1979), due to increased intravascular protein (albumin) by triggering the production of hepatic albumin and reuptake of electrolytes (sodium) (Convertino et al., 1980; Convertino, 1991; Fellmann, 1992; Nadel, 1996), increases in hormones that regulate fluid volume (e.g., aldosterone, arginine vasopressin, natriuretic atrial peptide (NAP) and renin-angiotensin)

(Convertino et al., 1980; Fellmann, 1992; Nagashima et al., 2000; Wade et al., 1985; Yang et al., 1998). Higher blood volume increases blood pressure and this results in increased shear stress in the vasculature (Birk et al., 2013; Laughlin et al., 2008). The increased heart rate during exercise stimulates contractility of heart rate by activation of the sympathetic nervous system, which also increases shear stress (BLAIR et al., 1961). These local hemodynamic changes activate endothelial mechanical-sensitive ion channels such as piezo1 channels and G-proteins, caveolin, and integrins. Mechanical signals lead to calcium entering, activation of endothelial nitric oxide synthase (eNOS) and the production of NO and endothelial-derived hyperpolarizing factor (EDHF) (Awolesi et al., 1994; Caolo et al., 2020; Green et al., 2004; Laughlin et al., 2008; Silva and Zanesco, 2010). NO contributes to approximately 30% increases in responses of cutaneous blood flow to Ach released during physical exercise (Boutsiouki et al., 2004; Holowatz et al., 2005; Kellogg Jr et al., 2005; Laughlin et al., 2008). For better regulation of core temperature, NO and hypoxia resulting from exercise can upregulate vascular endothelial growth factor (VEGF), which promotes microvascular numbers (angiogenesis) and increases capillary density that promotes cutaneous perfusion (Breen et al., 2008; Jensen et al., 2004; Lloyd et al., 2005; Michiels et al., 2000).

The optimization of vascular structure and improved blood flow distribution can attenuate some of the heat strain produced by coronavirus disease in patients with neurological disorders. Increases in antioxidant enzyme levels induced by exercise also assists in promoting skin vasodilation by improving NO bioavailability and reducing damage of lipid peroxidation-mediated damage of vascular endothelial cells (Dawson et al., 2013; Eskurza et al., 2004; Finaud et al., 2006; Holowatz et al., 2006; Leeuwenburgh and Heinecke, 2001; Tew et al., 2012; Violi et al., 1999). Chronic aerobic exercise increases the activity of vasodilatory mediators such as NO, prostacyclin, prostaglandins, bradykinin, and EDHF that promotes cutaneous perfusion and limits exercise-induced increases of core temperature (Colberg et al., 2009; Colberg et al., 2002; Gooding et al., 2006; Lenasi and Štrucl, 2008; Sokolnicki et al., 2007; Wang, 2005). In addition, these factors interact to enhance skin perfusion by increasing cutaneous flow produced by Ach (Gaubert et al., 2007; Lenasi and Strucl, 2004; Medow et al., 2008; Padilla et al., 2011; Wang, 2005). Increased insulin-induced tissue metabolism improves endothelial function induced by aerobic exercise by phosphorylating eNOS and increasing NO production (Ghafouri et al., 2011; Harris et al., 2008; Kashyap et al., 2005; Rossi et al., 2005), which activates $Ca^{2+}$-activated

potassium ($K^+$) channels (Bychkov et al., 1998; Kane et al., 2004; Merkus et al., 2006; Misurski et al., 2001) and ATP-sensitive $K^+$ channels (McKay and Hester, 1996).

Exercise and endurance training change body composition (reduce subcutaneous body fat), serum lipid and lipoproteins (increases high-density lipoprotein cholesterol [HDL-C]), and attenuates the oxidation of low-density lipoprotein cholesterol (LDL-C) (Gordon et al., 2014; Kodama et al., 2007; Kraus et al., 2002; Neves et al., 2017). Oxidation of LDL-C inhibits the release of NO and mitigates endothelium-dependent vasodilation (Liao et al., 1995). Exercise increases the expression of antioxidant enzymes such as superoxide dismutase (SOD), which increases the bioavailability of NO inhibition of LDL-C oxidation and enhances the vasodilatory sensitivity to chronic activation of β-adrenergic receptors on microvascular walls (Woodman et al., 2005; Woodman et al., 2004).

Plasma levels of adiponectin (APN) are increased by regular physical exercise (Saeidi et al., 2020; Zouhal et al. 2021). APN binds to adiponectin receptor 1 (AdipR1) in endothelial cells, mitigating the induction of inflammasomes, especially NLPR3, whose signals include activation of caspase-1 and IL-1β (Du et al., 2016; Hui et al., 2012; Lee et al., 2020; Lee et al., 2018; Lee et al., 2011). Downregulated inflammasomes attenuate ROS production in endothelial cells. Therefore, exercise training increases endothelial APN levels to promote NO production and its bioavailability, and reduces oxidative and apoptotic damage of microvessels (Chen et al., 2003; Gleeson et al., 2011; Moien-Afshari et al., 2008; Plant et al., 2008; Wang et al., 2018; Zhang et al., 2015).

Engaging in regular physical exercise leads to adaptations in the cardiovascular system and skeletal muscles, whereby less metabolic exertion is required to perform the same intensity of exercise (James et al., 2017; Lorenzo et al., 2010; Nadel et al., 1974; Pivarnik et al., 1987; Sawka et al., 1985). Exercise reduces vascular inflammation (Pedersen, 2009; Ribeiro et al., 2010), for example by releasing IL-6 (a myokine released by skeletal muscles into the circulation during physical exercise) (Jankord et al., 2007; Pedersen, 2009; Pedersen and Febbraio, 2008; Pedersen et al., 2004; Suzuki et al., 2020) to increase anti-inflammatory (IL-10, IL-1ra) and lower pro-inflammatory (TNF-α, IL-1β) cytokine levels (Pedersen, 2009; Shephard, 2002; Starkie et al., 2003; Suzuki, 2019).

Other mechanisms related to the beneficial effects of exercise in reducing core temperature includes the release of ATP by endothelial cells and erythrocytes (Ellsworth and Sprague, 2012;

Hellsten et al., 1998; Hellsten et al., 2012; Singel and Stamler, 2005). ATP, which is released during exercise and in response to hypoxia and shear stress, binds to P2Y receptors in micro-vessels to release NO and PGs (prostacyclin, $PGE_2$) (Burnstock et al., 2013; Corr and Burnstock, 1994; Frandsen et al., 2000; Hellsten et al., 1998; Huang et al., 2000; Mortensen et al., 2009a; Mortensen et al., 2009b; Nyberg, Michael et al., 2013) and hyperpolarization of vascular cells (Crecelius et al., 2012; Rosenmeier et al., 2008). Additionally, increased concentrations of plasma ATP during exercise inhibits sympathetic vasoconstriction of α-adrenergic receptors, a phenomenon known as functional sympatholysis (Kirby et al., 2008; Rosenmeier et al., 2004). Exercise, especially endurance training, attenuates the effects of endothelial-dependent vasoconstriction produced by endothelin-1 (Beck et al., 2013; Maeda et al., 2003; Nyberg, M et al., 2013; Nyberg et al., 2014), thromboxane $A_2$ (Hansen et al., 2011; Stergioulas and Filippou, 2006), and angiotensin II (Rush and Aultman, 2008; Zucker et al., 2015).

Adaptations in sweat rates may be important when monitoring body core temperature. Changes in response to exercise include increases in cholinergic sensitivity, greater rate and efficiency of eccrine glands in sweat production per gland, increased number and sensitivity of muscarinic receptors responsible for sweating, and reduced choline esterase activity (Lorenzo and Minson, 2010; Périard et al., 2016). Thus, exercise training can reduce the threshold for initiating cutaneous blood flow and sweat production in response to increases in core body temperature.

The majority of the vascular benefits produced by exercise training occur via increased NO bioavailability. Exercise-induced increases in NO inhibits virus replication by suppressing ribonucleotide reductase (Ellermann-Eriksen, 2005; Komatsu et al., 1999), and is supported by findings that NOS-deficient mice are more susceptible to viral infections (Gamba et al., 2004; MacLean et al., 1998).

Exercise-induced adaptations in thermoregulation occur within 3-14 days (Garrett et al., 2011), with the initial changes in the cardiovascular system associated with hypervolemia (Lorenzo et al., 2010; Nielsen et al., 1993; Shvartz et al., 1977; Weller et al., 2007) and secondary adaptations related to sweat production (Nielsen et al., 1993; Roberts et al., 1977; Shvartz et al., 1977; Wyndham et al., 1976). Light to moderate-intensity endurance training ($\geq$ 50% $VO_2max$) for at least one week optimal to stimulate these adaptations and restore body temperature to healthy levels (Lorenzo et al., 2010; Périard et al., 2015; Sawka et al., 1985). Furthermore, thermobalance during steady-state exercise occurs within 30-45 min and increases in body

temperature occur within 15-20 min of physical exercise (Kenny and Jay, 2011). Thus, exercise of at least 20 min is needed to promote thermoregulatory adaptations. Since MS patients are very sensitive to heat stress, with exacerbating clinical signs during and after infection with SARS-CoV-2 (Willis and Robertson, 2020), management of the risks associated with heat stress should include physical exercise using exercise/rest (intermittent exercise) protocols), with close monitoring of hydration and cool-down strategies.

## 4. Conclusions

We reviewed thermoregulation management following exercise training in MS patients infected with COVID-19. The mechanisms of exercise-induced vascular benefits involve increased eNOS bioavailability and the anti-inflammatory effects of NO. Regular physical exercise increases vasodilation sensitivity to maintain core body temperature by reducing the sweat threshold and increasing responses of cutaneous vessels. Exercise-induced adaptations in the cardiovascular system mitigates perceived exertion and fatigue during physical exercise through improved thermoregulation, allowing MS patients to better manage neurological signs during and after infection with SARS-CoV-2.

## Author Contributions

OR, BT, NZ and HZ conceptualized and wrote the first draft. AMT, IL, HZ, and OR developed the study concept. KG, KS, and HZ reviewed and edited the final version of manuscript. All authors contributed to the article and approved the submitted version.

## Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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