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Sympathetic regulation during thermal stress in human aging and disease

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Abstract

Humans control their core temperature within a narrow range via precise adjustments of the autonomic nervous system. In response to changing core and/or skin temperature, several critical thermoregulatory reflex effector responses are initiated and include shivering, sweating, and changes in cutaneous blood flow. Cutaneous vasomotor adjustments, mediated by modulations in sympathetic nerve activity (SNA), aid in the maintenance of thermal homeostasis during cold and heat stress since (1) they serve as the first line of defense of body temperature and are initiated before other thermoregulatory effectors, and (2) they are on the efferent arm of non-thermoregulatory reflex systems, aiding in the maintenance of blood pressure and organ perfusion. This review article highlights the sympathetic responses of humans to thermal stress, with a specific focus on primary aging as well as impairments that occur in both heart disease and type 2 diabetes mellitus. Age- and pathology-related changes in efferent muscle and skin SNA during cold and heat stress, measured directly in humans using microneurography, are discussed.

Keywords

sympathetic nervous system; microneurography; thermoregulation; heat; cold; diabetes

INTRODUCTION

As homeotherms, humans regulate core temperature within a narrow range around a theoretical “set point” (~37°C) via a series of integrated autonomic reflex mechanisms. The maintenance of thermal homeostasis requires increased heat dissipation during hyperthermia and increased conservation and/or generation of heat during hypothermia. Severe increases or decreases in body temperature (core or skin, or both) can challenge these regulatory systems and, if the challenge to thermal homeostasis (i.e., “thermal stress”) is sustained in

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duration or extreme in magnitude, may result in death (Berko et al., 2014; Bouchama et al., 2002; Collins et al., 1977). In response to thermal stress, humans invoke several critical thermoregulatory reflexes including piloerection, shivering, sweating, and profound changes in cutaneous blood flow. All of these efferent responses are controlled by higher brain centers, primarily the preoptic/anterior hypothalamus, which is considered to be the principal integration and control center for thermoregulation (Nakamura, 2011). In addition to thermoregulation, the integrated cardiovascular responses to thermal stress involve critical adjustments in autonomic activity to maintain blood pressure and organ perfusion (Charkoudian, 2010; Crandall et al., 2015; Holowatz et al., 2010b; Nakamura, 2011). Given that changes in skin blood flow occurring during thermal stress may have a significant impact on cardiac output and peripheral vascular resistance (Crandall et al., 2015; Kenney et al., 2003b; Rowell, 1986; Rowell, 1974), sympathetic regulation of cutaneous blood flow during thermal stress has received substantial research attention.

Individuals with altered sympathetic regulation during thermal stress, including older adults and those with various cardiovascular pathologies, have an attendant increased risk for heat- and cold-related morbidity and mortality (Conti et al., 2005; Curriero et al., 2002; Ellis, 1972; Kenney et al., 2014; Meiman et al., 2015; Semenza et al., 1996; Vandentorren et al., 2006). Understanding the mechanisms underlying impaired thermal-cardiovascular integration in this population has clear clinical implications. There are a multitude of disease states that increase in frequency and severity with aging, many of which are also associated with alterations in central sympathetic regulation. As such, studies aimed at understanding sympathetic neural regulation during thermal stress in these clinical populations (1) are important for delineating mechanisms of aberrant sympathetic neural control of the cardiovascular system and (2) may provide novel insight for therapeutic strategies to mitigate the increased risk posed by thermal challenges.

Given this background, the objective of this review is to highlight the sympathetic responses to thermal stress in humans, with a specific focus on neural control of blood pressure and cutaneous blood flow. Although sympathetic regulation of sweating and/or shivering is critical for the maintenance of thermal homeostasis, these responses are expertly reviewed elsewhere (Johnson et al., 2010). This review includes an emphasis on primary aging, as well as separate discussions of functional sympathetic alterations that occur in heart disease and type 2 diabetes mellitus. We have attempted to integrate animal and human studies to provide a comprehensive understanding of this area of research; however, the great majority of work comes from studies in humans, and therefore forms the basis of this review. While there is an abundance of research aimed at understanding the peripheral vascular and central cardiovascular mechanisms of human thermoregulation, these topics have been well covered elsewhere (Charkoudian, 2010; Crandall et al., 2015; Greaney et al., 2015a; Holowatz et al., 2010a; Holowatz et al., 2010b; Johnson et al., 2010; Johnson et al., 2014) and are outside the scope of this review. We have cited a number of reviews in an attempt to direct the reader to additional research in this field.

Measurement Techniques to Assess Sympathetic Function during Thermal Stress in Humans

There are several methods of determining sympathetic nervous system activity (SNA) (Charkoudian et al., 2014; Esler et al., 2003; Grassi et al., 1999). Global measures of SNA can be estimated from plasma or urine catecholamine concentrations; however, such indirect techniques do not account for the reuptake of norepinephrine (NE; the primary neurotransmitter released from postganglionic sympathetic nerves in response to neural firing) back into nerve terminals, extraneuronal NE metabolism, or NE clearance. To address these inherent methodological shortcomings, radiotracer techniques were developed, which allow for the determination of both global and organ-specific NE spillover rates (Esler et al., 2003; Grassi et al., 1999). Although these techniques represent powerful research tools that can be used to assess SNA from tissues such as the heart or the kidney, their utility is limited by both the invasiveness and associated technical challenges.

Microneurography, originally developed in the 1960s by Hagbarth and Vallbo (Hagbarth et al., 1968), has become the primary tool for studying human SNA. This approach can be used to selectively record efferent sympathetic outflow from postganglionic peripheral sympathetic nerve fibers; sympathetic recordings from the peroneal and ulnar nerves are common choices (Delius et al., 1972a). Multiunit postganglionic SNA typically occurs as bursts of impulses separated by silent periods of varying duration. Because these bursts occur in different temporal patterns and in response to differing stimuli/maneuvers in skin and muscle nerve fascicles (Delius et al., 1972a; Delius et al., 1972b), they can be reliably identified as either muscle (MSNA) or skin SNA (SSNA).

MSNA bursts mediate vasoconstriction and represent efferent sympathetic activity that is subject to powerful feedback from the arterial baroreceptors; thus, MSNA has a critical role in blood pressure regulation (Guyenet, 2006; Vallbo et al., 1979). MSNA recordings are strongly correlated with renal, cardiac, and whole-body NE spillover (Wallin et al., 1992; Wallin et al., 1996), further demonstrating its direct applicability as an index of central sympathetic outflow in humans. SSNA, on the other hand, may contain vasoconstrictor, piloerector, sudomotor, and/or vasodilator impulses within bursts of activity (Charkoudian et al., 2014; Vallbo et al., 1979). Because the cutaneous circulation is the primary effector organ for thermoregulation, SSNA (via its regulation of the skin vasculature and sweat glands) has a central role in maintaining thermal homeostasis (Charkoudian et al., 2014). However, given the methodological challenges associated with the analysis and interpretation of SSNA—including the lack of cardiac rhythmicity, the irregular shape and bursting pattern, and the potential for multiple different types of impulses to be contained within a single burst of activity—relatively few studies have examined efferent SSNA during thermal challenges in humans. Nevertheless, much of the information regarding sympathetic regulation during thermal stress has been determined using microneurographic recordings and many of these studies will be highlighted in this review.

Sympathetic Regulation during Cold Stress

Efferent Sympathetic Outflow during Whole-Body Cooling in Young Adults

The sympathetic thermoregulatory reflexes responsible for maintaining core temperature during cold exposure are activated when mean skin temperature decreases from a thermoneutral temperature of $\sim 34^{\circ}\text{C}$. Whole-body cooling-induced decreases in mean skin temperature elicit a pronounced systemic pressor response in healthy young adults (Cui et al., 2007; Cui et al., 2005b; Durand et al., 2004; Greaney et al., 2014; Hess et al., 2009; Wilson et al., 2007); a similar pressor response also occurs during more severe cold stress during which reductions in core temperature are observed (Collins et al., 1985; Inoue et al., 1992; Wagner et al., 1985). The pressor response to cooling is likely mediated by increases in sympathetic activation, because skin surface cooling increases total peripheral resistance without altering cardiac output (Cui et al., 2005b; Durand et al., 2004; Raven et al., 1980). Further, cold stress increases indirect indices of sympathetic nervous system activation (e.g., plasma NE) in young adults (Durand et al., 2004; Frank et al., 2000). Interestingly, findings from studies employing direct measures of MSNA during whole-body cooling in young adults are equivocal (Cui et al., 2007; Fagius et al., 1991; Greaney et al., 2014). For example, studies in which skin surface cooling was induced via a water-perfused suit (to decrease mean skin temperature from a thermoneutral of ~ 34 to $\sim 30^{\circ}\text{C}$ and without any reduction in core temperature) reported no change in MSNA during cold exposure (Cui et al., 2007; Greaney et al., 2014). However, an increase in MSNA throughout cooling has been reported in studies in which participants were positioned in a temperature controlled box and exposed to low ambient air temperatures of $\sim 10^{\circ}\text{C}$ (Fagius et al., 1991). Although skin and core temperatures were not reported in the study by Fagius *et al.*, making direct comparisons between studies difficult, the most likely explanation for these conflicting findings relates to methodological differences by which the cold stress was applied, as well as the relative intensity of the cold stimulus. Skin surface cooling using a water-perfused suit is a well-controlled stimulus, which allows for precise reductions in mean skin temperature, typically without eliciting shivering or decreases in core temperature (Cui et al., 2007; Greaney et al., 2014). While exposure to cold ambient air may be more ecologically valid, it may also induce profound facial cooling, which is known to be a strong stimulus for MSNA (Heindl et al., 2004). In experimental paradigms employing a water-perfused suit, the face is typically not covered and is thus only exposed to thermoneutral ambient air. Taken together, these apparent contrasting conclusions regarding the MSNA response to whole-body cooling suggest that the sympathetic activation that occurs during cold stress is intensity dependent and likely influenced by the populations of thermal and/or pain receptors that are stimulated.

Because MSNA is primarily under baroreflex control (Guyenet, 2006; Sundlof et al., 1978b; Wallin et al., 1988), it is perhaps surprising that skin surface cooling increases blood pressure without altering MSNA. This scenario suggests a resetting of the operating point of baroreflex control of MSNA to elevated blood pressures. Cui *et al.* (Cui et al., 2007) examined baroreflex control of MSNA during pharmacologically-induced changes in blood pressure. The authors reported that the operating point of the baroreflex curve, defined as the mean MSNA and diastolic blood pressure during thermoneutrality and during cold stress, was shifted rightward to operate around the cooling-induced increase in blood pressure (Cui

et al., 2007). This presumably allows for adequate baroreflex-mediated buffering if blood pressure is further increased during cold stress, such as with the addition of exercise (Cui et al., 2007; Greaney et al., 2014). This rightward shift in the operating point during cold stress occurred without a change in the sensitivity of baroreflex control of MSNA (i.e., the slope of the relation between MSNA and diastolic blood pressure) (Cui et al., 2007); a finding that was also recently noted during spontaneous fluctuations in blood pressure (Greaney et al., 2014).

In the absence of the aforementioned resetting, MSNA would be decreased in the face of increased arterial pressure, thereby buffering the cooling-induced pressor response. Instead, the maintenance of higher pressures during whole-body cooling provides a larger buffer for decreased arterial blood pressure during cardiovascular challenges to blood pressure regulation such as orthostasis. Tolerance to orthostatic stress is significantly influenced by thermal stress, as well as by a variety of pathological conditions (Brothers et al., 2011; Keller et al., 2009), including autonomic dysfunction (Harms et al., 2000). Multiple studies have demonstrated that skin surface cooling preserves blood pressure during an orthostatic challenge thereby improving orthostatic tolerance (Cui et al., 2007; Cui et al., 2005b; Durand et al., 2004; Lind et al., 1968; Raven et al., 1981; Raven et al., 1980). Thus, the cold-induced resetting of the operating point of the baroreflex curve may aid in preserving blood pressure during an orthostatic challenge before ensuing syncopal symptoms (Cui et al., 2007). Collectively, the evidence in healthy young adults suggests that the sympathetic outflow directed to the muscle vasculature importantly contributes to the integrated cardiovascular adjustments during cold exposure.

Autonomic nervous system control of the cutaneous circulation is of critical importance for human thermoregulation. During cold exposure, reductions in skin blood flow decrease convective heat loss and increase tissue insulation, thereby minimizing changes in core temperature and preventing hypothermia. Sympathetic adrenergic nerve fibers modulate vascular tone during normothermia as well as the vasoconstriction that occurs in response to cold exposure (Johnson et al., 2014). Afferent sensory input from peripheral thermosensors in the skin is integrated centrally in the preoptic/anterior hypothalamus, subsequently eliciting peripheral cutaneous vasoconstriction via increased efferent SSNA (Boulant, 2006; Gibbins et al., 2003). During skin surface cooling, skin blood flow can decrease to a physiological minimum, after which further cooling will not induce additional vasoconstriction (Rowell, 1986). Moreover, reflex cutaneous vasoconstriction is graded in accordance with stimulus intensity (Holowatz et al., 2010b), such that during severe cold stress, skin blood flow can approach zero (Johnson et al., 2014; Rowell, 1986).

In contrast to the lack of a MSNA response to whole-body cooling, decreases in mean skin temperature evoke robust increases in efferent SSNA in young adults (Cui et al., 2006; Grassi et al., 2003; Greaney et al., 2015b; Sawasaki et al., 2001; Strom et al., 2011). An increase in SSNA has been observed during acute (~3-4 min) (Strom et al., 2011) and prolonged (~30 min) (Cui et al., 2006; Grassi et al., 2003; Greaney et al., 2015b) whole-body cooling protocols. Further, these increases were apparent when normalized to and expressed as a percentage increase from baseline (Greaney et al., 2015b), when normalized and expressed as an absolute increase from baseline (Strom et al., 2011), and when analyzed

using spectral components of the integrated SSNA signal (Cui et al., 2006). Further, the increases in SSNA during cold stress were tightly correlated with subsequent reductions in cutaneous blood flow in the area of neural innervation (Greaney et al., 2015b), indicating that this adrenergic vasoconstrictor neural stimulus is likely responsible for evoking the reflex reductions in peripheral skin blood flow during whole-body cold exposure (Bini et al., 1980; Charkoudian et al., 2014). These differential findings regarding sympathetic outflow directed to muscle and skin during cold stress are not surprising given the functional selectivity and differentiation of sympathetic nerve traffic (Charkoudian et al., 2014).

Alterations in Efferent Sympathetic Outflow in Aging

Physiological responses to moderate cold stress are altered in healthy older adults, and even during mild cold stress (e.g., ambient temperature = 22°C), older adults exhibit a relative inability to defend core temperature (Degroot et al., 2007). Core temperature-reducing cold stress typically elicits augmented pressor responses in older adults (Collins et al., 1985; Inoue et al., 1992; Wagner et al., 1985), though this is not a universal finding (Budd et al., 1991; Degroot et al., 2007). An exaggerated increase in blood pressure in older adults has also been reported during milder cold stress even in the absence of a reduction in core temperature (Greaney et al., 2014; Hess et al., 2009; Wilson et al., 2010). Exposure to a moderate intensity of cooling is likely more indicative of the typical cold stress encountered by older adults during activities of daily living (Hess et al., 2009) and may therefore have greater clinical relevance. The age-related augmentation in the pressor response during cold exposure is not mediated by an increase in cardiac output (Wilson et al., 2010). Rather, the response appears to be mediated by increased peripheral vascular resistance, as the exaggerated increase in blood pressure is associated with both increased central arterial stiffness (Hess et al., 2009) and increased left ventricular preload (Wilson et al., 2010). The greater increase in left ventricular filling pressure in older adults (Wilson et al., 2010) may suggest that augmented vasoconstriction occurs in vascular beds other than the skin (e.g., skeletal muscle or visceral vascular beds) (Greaney et al., 2015b; Thompson et al., 2005; Thompson et al., 2004).

Consistent with these age differences in cardiovascular responses, whole-body cold stress elicits pronounced increases in MSNA in older, but not young, adults (Fig. 1) (Greaney et al., 2014). This increase in MSNA during whole-body cooling in older adults may directly contribute to the augmented pressor response to this thermal stimulus. Another mechanism that may underlie the exaggerated neural cardiovascular responses to cold stress is reduced buffering of the increases in MSNA by the baroreflex, either via the lack of a cold-induced shift in the operating point of the baroreflex curve or by an alteration in the sensitivity of baroreflex control of MSNA. However, as in young adults, there does not appear to be a change in the sensitivity of arterial baroreflex control of MSNA. This conclusion is based on an analysis of the relation between spontaneously occurring variations in diastolic blood pressure and MSNA during whole-body cooling in older adults (Greaney et al., 2014). Although these data provide initial support for preserved sympathetic baroreflex function during cold exposure in healthy aging, future studies designed to more specifically examine potential age-related changes in arterial baroreflex function, including potential alterations in parameters of the full stimulus-response curve for the baroreflex, are warranted.

Thermoregulatory control of skin blood flow is markedly impaired in healthy older adults, such that for a given decrease in mean skin temperature, reflex cutaneous vasoconstriction is significantly attenuated (Degroot et al., 2007; Frank et al., 2000; Greaney et al., 2015b; Lang et al., 2009; Stanhewicz et al., 2013; Thompson et al., 2004). This deficit has been documented and characterized in detail in a number of studies employing various experimental paradigms to induce cold stress and multiple methods to measure skin blood flow. Cumulatively, these studies demonstrate that pronounced age-related cutaneous vascular dysfunction contributes to impaired thermoregulation in aged populations; the interested reader is directed to several excellent reviews (Holowatz et al., 2010a; Holowatz et al., 2010b; Johnson et al., 2014).

Compromised thermoregulatory vasoconstriction in aged skin has been linked to functional impairments at multiple points along the efferent neural reflex axis (Greaney et al., 2015b; Holowatz et al., 2010a; Holowatz et al., 2010b; Stanhewicz et al., 2013; Thompson et al., 2005; Thompson et al., 2004). Such deficits include age-related alterations in sympathetic outflow directed to the skin vasculature, as evidenced by studies demonstrating that the SSNA response to whole-body cooling was substantially reduced in healthy older adults (Fig. 2) (Grassi et al., 2003; Greaney et al., 2015b). Further, the blunted efferent SSNA response to cooling was closely correlated with age-related impairments in reflex cutaneous vasoconstriction in the area of neural innervation (Greaney et al., 2015b). Interestingly, the slope of the relation between SSNA and cutaneous blood flow was not different between young and older adults in that study (Greaney et al., 2015b). Taken together, these data suggest that the inability of older adults to appropriately decrease skin blood flow during cooling is not a result of diminished sensitivity of the reflex response, but instead reflects an age-related reduction in the range of efferent SSNA outflow elicited by cooling.

Greaney *et al.* (Greaney et al., 2015b) recently examined potential age-related alterations in the central ability to elicit skin sympathetic outflow by additionally assessing SSNA during the non-thermoregulatory stimulus of mental stress, both at thermoneutrality and when superimposed on whole-body cooling. In addition to thermoregulatory challenges, SSNA is highly responsive to arousal stimuli and psychological stress (Charkoudian et al., 2014), as mental stress elicits sustained and reproducible increases in SSNA in young adults (Muller et al., 2013a; Muller et al., 2013b). Aged adults exhibited robust increases in SSNA during mental stress superimposed on whole-body cooling (Greaney et al., 2015b), indicating that a central inability to elicit further increases in SSNA does not explain the lack of an increase in skin sympathetic outflow during cooling in healthy aging (Greaney et al., 2015b). Instead, alterations in either afferent signal from cutaneous thermoreceptors or central integration of converging signals at the level of the hypothalamus, or both, mediate the age-related deficits in efferent SSNA during whole-body cold stress.

Alterations in Efferent Sympathetic Outflow in Heart Failure and Diabetes

The presence of overt cardiovascular pathology in older adults further modifies sympathetic regulation during cold exposure, and alterations in central sympathetic regulation likely contribute to impaired effector responses to thermal stress. However, few studies have examined efferent sympathetic outflow in response to cold stress in cardiovascular

pathologies, and thus the discussion below is limited. For instance, a classic study performed by Zelis *et al.* (Zelis et al., 1969) demonstrated that the cutaneous vascular bed is abnormally constricted at rest in adults with heart failure, and in these patients there is also excessive cutaneous vasoconstriction during, and acutely following, dynamic exercise. While these data indirectly suggest potential alterations in efferent SSNA in response to perturbations that challenge cardiovascular homeostasis, to our knowledge, no studies have examined efferent SNA responsiveness (muscle or skin) during whole-body cold stress in patients with heart failure. This area of research is clinically important given the significant increase in morbidity and mortality in heart failure patients in the winter months (Stewart et al., 2002).

The thermoregulatory responses to cold stress are likewise altered in individuals with type 2 diabetes mellitus (Sokolnicki et al., 2009; Strom et al., 2011; Wick et al., 2006), likely due in part to progressive decrements in peripheral nerve function. Studies report that individuals with type 2 diabetes mellitus had higher basal cutaneous vascular conductance compared to healthy adults, a difference that was abolished by application of bretylium tosylate to block the presynaptic release of neurotransmitters from adrenergic nerve terminals (Wick et al., 2006), suggesting reduced resting sympathetic vasoconstrictor tone in diabetes. Only one study has examined the integrated physiological responses to whole-body cooling in individuals with type 2 diabetes mellitus (Strom et al., 2011), reporting similar SSNA and cutaneous vasoconstrictor responses to rapid whole-body cooling compared to age- and body size-matched healthy adults (Strom et al., 2011). Although similar vasoconstrictor responsiveness to cooling in type 2 diabetes may be surprising in the face of the noted vascular dysfunction characteristic of the disease (Sokolnicki et al., 2007; Sokolnicki et al., 2009), the rapid cooling paradigm that was utilized is thought to evoke greater release of the large, dense core vesicles containing sympathetic co-transmitter(s) in addition to NE (Bartfai et al., 1988; Lundberg, 1996). Interestingly, the authors reported an increase in SSNA of approximately 50% during rapid cooling in both subject groups (Strom et al., 2011), and although methodological differences make direct comparisons between studies difficult, this reported increase in SSNA is similar in magnitude to the substantially blunted increase in SSNA in healthy older (~55 yrs) compared to young adults discussed above (Greaney et al., 2015b). Thus, the SSNA response to cold stress appears to be preserved in type 2 diabetes.

In contrast to the preservation of the SSNA response during rapid body cooling in individuals with diabetes noted above, a smaller increase in blood pressure was noted in these patients (Strom et al., 2011). Although MSNA at rest is higher in individuals with type 2 diabetes without evidence of neuropathy, MSNA responsiveness to a cold pressor test was not different from responses noted in healthy adults (Huggett et al., 2005). However, whether the attenuated pressor response to systemic whole-body cold stress is a result of blunted increases in MSNA remains unclear, and a comprehensive examination of the sympathetic neural mechanisms of blood pressure regulation during cold stress in diabetic patients merits further investigation. It is important to note that the individuals with diabetes studied in the aforementioned investigations were relatively healthy, with well-controlled glucose and without clinically significant comorbidities. Thus, future studies examining the sympathetic regulation during cold stress in 'less healthy' individuals with diabetes are warranted.

Sympathetic Regulation during Passive Heat Stress

Efferent Sympathetic Outflow during Whole-Body Heating in Young Adults

In young adults, whole-body heat stress evokes a series of highly coordinated cardiovascular responses that are necessary to promote the transfer of heat between the body and the surrounding environment to maintain thermal homeostasis. These cardiovascular responses include considerable increases in cardiac output and a redistribution of blood from the renal and splanchnic circulations which combine to facilitate a substantial increase in skin blood flow (Crandall et al., 2015; Kenney et al., 2003b; Rowell, 1986; Rowell, 1974). At the onset of heat stress as internal temperature rises, skin blood flow increases due to passive vasodilation (i.e., the withdrawal of vasoconstrictor tone) (Kellogg et al., 1995). With further increases in internal temperature, the active vasodilator system is activated, with is mediated by sympathetic cholinergic nerves, and involves the co-release of peptidergic neurotransmitter(s) along with acetylcholine (Kellogg et al., 1995). Precise adjustments of the autonomic nervous system are critical in mediating the cardiovascular and thermoregulatory response to heat stress. A number of excellent reviews on thermoregulation during heat stress, including the influence of primary aging, have previously been published (Crandall et al., 2015; Rowell, 1986; Rowell, 1974). Given those comprehensive reviews, the focus here will be on the sympathetic responses to passive heat stress, defined as exogenous heat gain while metabolism remains near basal levels. Studies evaluating responses to exercise-induced heat stress, during which significant increases in metabolism occur, are outside the scope of this review, as exercise induces multiple physiological responses not directly resulting from increased body temperature *per se*.

Passive whole-body heat stress is a substantial sympathoexcitatory stimulus (Rowell, 1990) evoking a 40-90% increase in MSNA in healthy young adults (Crandall et al., 2003; Cui et al., 2009; Cui et al., 2010; Cui et al., 2011; Cui et al., 2002a; Cui et al., 2004a; Gagnon et al., 2015; Keller et al., 2006; Low et al., 2011; Niimi et al., 1997). This sympathoexcitation is directly related to stimulus intensity, as continued elevations in MSNA were observed when core temperature was further increased (Low et al., 2011; Niimi et al., 1997). These findings in healthy humans are consistent with the progressive increases in renal, lumbar, and splanchnic sympathetic nerve activity across a wider range of elevations in core temperature (3°C) during passive heating in rodent models (Kenney et al., 1995; Kenney et al., 1998; Kenney et al., 2002). It has been postulated that these increases in MSNA during passive heat stress reflect general systemic sympathetic activation that is largely responsible for driving the increased cardiac output and visceral blood redistribution (Low et al., 2011). Passive heating has been reported to have little effect on muscle blood flow (Edholm et al., 1956; Heinonen et al., 2011; Roddie et al., 1956) despite the dramatic increase in MSNA. However, the net systemic increase in sympathetic activation is a crucial determinant of the blood flow redistribution that occurs during heat stress (Rowell, 1984).

Several modulators of MSNA have been proposed to contribute to the noted sympathoexcitation during passive heat stress, including decreased body water content, baroreceptor unloading, and increased ventilation, all of which have been demonstrated to independently increase MSNA (Rabbits et al., 2009; Seals et al., 1993; Sundlof et al.,

1978a). However, the MSNA response to passive heating occurs during increases in core temperature that are generally not associated with changes in arterial blood pressure or ventilation (Low et al., 2011; Niimi et al., 1997). Moreover, the increases in MSNA were not reversed during baroreceptor loading when a rapid saline infusion was superimposed on heat stress (Crandall et al., 1999), suggesting that the MSNA response to passive heating is independent of the baroreflex. Furthermore, heat stress in humans does not alter the slope of the relation between changes in MSNA and acute (Cui et al., 2002a) or sustained (Cui et al., 2002b) pharmacologically-induced changes in diastolic blood pressure, suggesting that heat stress does not affect the sensitivity of arterial baroreflex control of MSNA. Instead, this thermal stimulus shifted the baroreflex curve to operate around the heat-induced increase in MSNA (Cui et al., 2002a). However, using analyses based upon spontaneous fluctuations in arterial pressure, Keller *et. al.* (Keller et al., 2006) recently demonstrated that whole-body heating enhanced arterial baroreflex control of MSNA through increased sensitivity of the 'gating' mechanism, such that for a given decrease in diastolic pressure there was a greater increase in burst incidence, but not burst area, during hyperthermia relative to normothermia. The reason for these contrasting study conclusions are unclear, but may relate to methodological differences between studies. Interestingly, the passive heating-induced increase in MSNA is exaggerated, not attenuated, during lower body negative pressure (Cui et al., 2004a). During this orthostatic challenge in the heat, the slope of the relation between the increase in MSNA relative to the reduction in central venous pressure was greater than during normothermia (Cui et al., 2004a), a finding consistent with the hypothesis outlined above that heat stress increases the sensitivity of a "gating" mechanism regulating the frequency of sympathetic neural firing (Keller et al., 2006). Collectively, this series of studies suggests that arterial baroreceptor modulation of MSNA remains intact during heat stress (Crandall et al., 2003; Cui et al., 2002a; Low et al., 2011). Thus, the heat-stress induced increase in MSNA appears likely to be mediated via direct heat-induced central activation of the sympathetic nervous system (Kenney et al., 2002; Kenney et al., 2003a; Kenney et al., 2011; Kenney et al., 2000); however, the specific neural mechanisms responsible for the increased sympathetic activity during heat stress in humans are not known.

In addition to MSNA, whole-body passive heating also influences SSNA in healthy young adults. As indicated above, multiunit SSNA recordings comprise vasoconstrictor, sudomotor, and active vasodilator fibers (Bini et al., 1980; Hagbarth et al., 1972). At the onset of heating, reductions in SSNA occur (Bini et al., 1980; Cui et al., 2006; Grassi et al., 2003), consistent with the withdrawal of vasoconstrictor tone. During more pronounced and sustained passive heating, robust increases in SSNA have been noted in most (Bini et al., 1980; Cui et al., 2006; Low et al., 2011; Wilson et al., 2001), but not all (Grassi et al., 2003), previous studies, presumably reflecting increases in both sudomotor and vasodilator neural activity. Grassi *et. al.* (Grassi et al., 2003) reported progressive reductions in SSNA throughout passive heating in young adults; however, the heating stimulus in that study (ambient air) was not well controlled. As with MSNA, the increase in SSNA is also related to stimulus intensity, as SSNA continued to increase during more severe increases (~1.9°C) in core temperature (Low et al., 2011). Thus, the cumulative evidence demonstrates robust increases in both MSNA and SSNA during passive whole-body heat stress in young adults.

At thermoneutrality, the baroreflex is not thought to modulate SSNA (Bini et al., 1981; Delius et al., 1972b; Hagbarth et al., 1972; Vissing et al., 1994; Wallin et al., 1975; Wilson et al., 2001). However, during heat stress, a large increase in skin blood flow occurs (Rowell, 1974; Rowell, 1984), such that baroreflex control of cutaneous vascular conductance may become important for the maintenance of blood pressure. Thus, because increases in skin blood flow during passive heating result from SSNA activity that is not present under normothermic conditions (when SSNA is primary vasoconstrictor in origin (Bini et al., 1980)), it is conceivable that the baroreceptors become capable of modulating SSNA during this thermal stress. However, studies investigating this research question have yielded equivocal results. Dodt *et. al.* (Dodt et al., 1995) reported decreases in SSNA during lower body negative pressure and upright tilt in heated individuals, suggesting that baroreceptor unloading can reduce SSNA during heat stress. In support of this concept, SSNA has been reported to display cardiac rhythmicity in moderately heated individuals (Bini et al., 1981; Macefield et al., 1996). In contrast, Cui *et. al.* (Cui et al., 2004b) demonstrated that baroreceptor unloading via low and moderate levels of lower body negative pressure during heat stress did not alter SSNA. Consistent with these findings, in heat stressed young adults pharmacologically-induced changes in blood pressure to load and unload the baroreceptors did not alter SSNA (Wilson et al., 2001). The reason(s) for these apparent discrepant findings is unclear; therefore, future studies aimed to delineate the potential role for the baroreflex in modulating SSNA during heat stress are necessary.

Alterations in Efferent Sympathetic Outflow in Aging

Neurally-mediated cardiovascular responses to passive heating are substantially altered in healthy human aging, with older adults demonstrating a blunted increase in cardiac output and less visceral vasoconstriction, both of which contribute to a markedly attenuated increase in cutaneous blood flow (Holowatz et al., 2010a; Holowatz et al., 2010b; Johnson et al., 1986; Johnson et al., 2014; Kenney et al., 2014; Kenney et al., 2003b). Despite these impairments, blood pressure is relatively well-maintained during heating in aged adults (Minson et al., 1998). Thus, given the pronounced alterations in the integrated cardiovascular responses to heating, it is conceivable that attenuations in sympathetic activity during heat stress also occur with healthy aging. Perhaps surprisingly, the increases in MSNA and plasma NE during passive heat stress were not different in older compared to young adults (Fig. 3) (Gagnon et al., 2015). Further, healthy human aging did not affect MSNA responsiveness to sympathoexcitatory perturbations (cold pressor test and lower body negative pressure) superimposed on heat stress (Gagnon et al., 2015). Taken together, these findings suggest that the impaired cardiovascular responses to passive heating in healthy human aging are likely not the result of blunted increases in sympathetic activity and instead indicate age-related alterations in adrenergic responsiveness and/or cardiac function.

Reflex cutaneous vasodilation is markedly impaired in healthy older adults, due in large part to age-related reductions in functional peptidergic cotransmitter(s) and nitric oxide bioavailability and subsequent cutaneous vascular dysfunction (Holowatz et al., 2003), as has been extensively reviewed elsewhere (Holowatz et al., 2010a; Holowatz et al., 2010b). However, few studies have examined the potential for age-related alterations in SSNA responsiveness during passive heating to contribute to this relative inability to appropriately

increase skin blood flow. To date, only one study has examined SSNA during heating, reporting lower absolute non-normalized SSNA responsiveness to mild (+8°C) increases in ambient room temperature in aged adults (Grassi et al., 2003), a thermal stimulus that likely did not change core temperature. In that study, age-related reductions in basal SSNA were also reported, and those baseline differences were not accounted for when examining SSNA during heating. In addition, the lack of appropriate data normalization procedures for SSNA make interpretation of these data challenging, especially in light of the progressive decline in SSNA during heating that was observed in all subject groups (Grassi et al., 2003). This finding is in direct contrast to the pronounced increases in SSNA reported during whole-body heating protocols using a water-perfused suit that were designed to elicit precise increases in core temperature (Bini et al., 1980; Cui et al., 2006; Low et al., 2011; Wilson et al., 2001). As such, future research aimed at more comprehensively examining SSNA responsiveness during passive heat stress is warranted. Further, although aging has been associated with a decreased ability of the cardiopulmonary baroreceptors to reflexively modulate skin blood flow during upright tilt in the heat (Scremin et al., 2004), a potential role, if any, of altered baroreceptor control of SSNA in mediating these impaired cutaneous vascular responses remains to be determined.

Alterations in Efferent Sympathetic Outflow in Heart Failure and Diabetes

In patients with cardiovascular pathology, adverse cardiac events are more likely to occur in the summer months (Aronow et al., 2004; Semenza et al., 1996). Additionally, the number of deaths linked to periods of extreme heat is much greater than those attributable to heat stroke alone, with the difference reflecting the fact that an overwhelming majority of excess deaths during heat waves report cardiovascular complications as the underlying cause (Kaiser et al., 2007). Thus, patients with cardiovascular disease, such as congestive heart failure, may be particularly vulnerable during prolonged heat exposure (Aronow et al., 2004), likely due to impairments in the thermoregulatory responses to heat stress. Heart failure is characterized by significant alterations in central sympathetic outflow (Grassi et al., 1995; Leimbach et al., 1986), as well as impairments in baroreflex function (Grassi et al., 1995). Cutaneous vasodilatory capacity at rest and during exercise are reduced in patients with heart failure (Zelis et al., 1969), an impairment that may contribute to heat intolerance. Indeed, subsequent studies have demonstrated an attenuated cutaneous active vasodilator response to whole-body passive heat stress (Fig. 4) (Cui et al., 2005a; Cui et al., 2013; Green et al., 2006). However, the increase in SSNA during passive heating in heart failure patients is not different from the responses of healthy adults (Fig. 4) (Cui et al., 2013), suggesting that attenuated increases in sympathetic outflow directed to the skin do not contribute to impaired thermoregulation in heart failure. Moreover, the sweating response to passive heating is preserved in human heart failure (Fig. 4) (Cui et al., 2005a; Cui et al., 2013; Green et al., 2006), indicative of intact efferent sympathetic cholinergic innervation and sweat gland function and providing further support for appropriate autonomic thermoregulatory function in heart failure. To date, no study has examined the MSNA response to whole-body passive heating in this clinical population.

As noted above, individuals with type 2 diabetes mellitus are also characterized by marked impairments in thermoregulatory function (Sokolnicki et al., 2009; Strom et al., 2011; Wick

et al., 2006). Patients with type 2 diabetes displayed delayed thresholds for the onset of cutaneous vasodilation, as well as attenuated cutaneous vasodilator responses throughout passive heating (Sokolnicki et al., 2009; Wick et al., 2006). Using bretylium iontophoresis to block the release of sympathetic adrenergic neurotransmitters and isolate the sympathetic active vasodilator system, Wick *et. al.* (Wick et al., 2006) demonstrated that the diabetes-induced alteration in the threshold for vasodilation resulted from a shift in control of active vasodilation to higher temperatures. These findings provide indirect support for the hypothesis that altered central sympathetic neural control mechanisms functionally contribute to impaired thermoregulation in diabetes; however, this premise remains to be confirmed with studies employing direct recordings of both MSNA and SSNA during passive heat stress in these patients.

Conclusions and Future Directions

Thermal stress severely challenges physiological homeostasis, and critical adjustments in sympathetic nervous system function are required for an appropriate cardiovascular and thermoregulatory response in order to maintain thermal homeostasis, blood pressure, and critical organ perfusion (Charkoudian, 2010; Crandall et al., 2015; Holowatz et al., 2010b; Nakamura, 2011). Several recent studies have illustrated that sympathetic regulation during passive cold and heat stress is altered in healthy human aging. These findings have clear clinical relevance, as the aged—with or without cardiovascular co-morbidities—contribute disproportionately to cold and heat-related cardiovascular deaths. These recent advances in our understanding of the sympathetic neural mechanisms mediating impaired thermoregulation during thermal stress in healthy older adults form the groundwork for elucidating potential alterations in sympathetic neural control of the vasculature in cardiovascular pathophysiology. Future studies are warranted to examine potential mechanistic alterations in sympathetic regulation during thermal stress in clinical populations.

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HIGHLIGHTS

- Thermoregulatory and non-thermoregulatory reflexes mediate the integrated cardiovascular responses to thermal stress via precise adjustments in sympathetic nervous system activity.
- Sympathetic regulation during thermal stress is profoundly altered in healthy human aging, resulting in impaired thermal-cardiovascular responses to environmental stressors and an increased risk of cold- and heat-related mortality.
- Heart failure and diabetes are clinical pathologies also associated with impaired sympathetic neural regulation during thermal stress.

Figure 1.

Muscle sympathetic nerve activity (MSNA) burst frequency was greater in older adults (open symbols) at thermoneutrality [mean skin temperature (T_{sk}) 34.0°C] and at each 0.5°C decrease in mean T_{sk} throughout whole-body cooling compared to young adults (filled symbols) (Panel A). Further, MSNA increased during cold stress in older but not young adults, reflected by the increase in MSNA burst frequency from baseline (i.e., mean T_{sk} 34.0°C) to mean T_{sk} 30.5°C (Panel B). * $P < 0.05$ vs. young; † $P < 0.05$ vs. mean T_{sk} 34.0°C. [Figure adapted with permission from (Greaney et al., 2014)].

Figure 2.

Whole-body cold stress [(i.e., gradual reduction in mean skin temperature (T_{sk}) from 34.0°C to 30.5°C] elicited robust and progressive increases in skin sympathetic nerve activity (SSNA; SSNA total activity) in young but not older adults (Panel A). The total increase in SSNA from baseline (i.e., mean T_{sk} 34.0°C) to mean T_{sk} 30.5°C is presented in Panel B.

* $P < 0.05$ vs. older; † $P < 0.05$ vs. mean T_{sk} 34.0°C. [Figure adapted with permission from John Wiley and Sons Publishing (Greaney et al., 2015b)].

Figure 3.

Whole-body passive heat stress sufficient to elevate core temperature by 0.6°C and 1.2°C increased muscle sympathetic nerve activity [MSNA; burst frequency (left panel) and burst incidence (right panel)] similarly in both healthy young (open symbols) and aged adults (filled symbols. *P<0.05 v. baseline; †P<0.05 vs. aged. [Figure reprinted with permission from John Wiley and Sons Publishing (Gagnon et al., 2015)].

Figure 4.

Reflex cutaneous vasodilation during whole-body heat stress (WBH) was blunted in congestive heart failure (CHF; filled bars; upper left panel). The increase in skin sympathetic nerve activity [SSNA; burst frequency (upper right panel) and total activity (lower right panel) during WBH was not different between control subjects (open bars) and those with CHF. There were no group differences in the sweating response to WBH (lower left panel). * $P < 0.05$ vs. baseline; † $P < 0.05$ vs. control. [Figure reprinted with permission from Wolters Kluwer Health, Inc. (Cui et al., 2013)].