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Review

# 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.



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## 1. 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

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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 duration or extreme in magnitude, may result in death (Berko et al., 2014; Bouchama and Knochel, 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 and Wilson, 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 and Wilson, 2015; Kenney and Munce, 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 and Kellogg, 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 and Wilson, 2015; Greaney et al., 2015a; Holowatz and Kenney, 2010a; Holowatz et al., 2010b; Johnson and Kellogg, 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.

### 1.1. Measurement techniques to assess sympathetic function during thermal stress in humans

There are several methods of determining sympathetic nervous system activity (SNA) (Charkoudian and Wallin, 2014; Esler et al., 2003; Grassi and Esler, 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 and Esler, 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 (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 and Wallin, 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 and Wallin, 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.

### 1.2. Sympathetic regulation during cold stress

#### 1.2.1. 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 ~34 °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 and Horvath, 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 and Kay, 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