Mechanisms of orthostatic intolerance during heat stress

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Abstract

Heat stress profoundly and unanimously reduces orthostatic tolerance. This review aims to provide an overview of the numerous and multifactorial mechanisms by which this occurs in humans. Potential causal factors include changes in arterial and venous vascular resistance and blood distribution, and the modulation of cardiac output, all of which contribute to the inability to maintain cerebral perfusion during heat and orthostatic stress. A number of countermeasures have been established to improve orthostatic tolerance during heat stress, which alleviate heat stress induced central hypovolemia (e.g., volume expansion) and/or increase peripheral vascular resistance (e.g., skin cooling). Unfortunately, these countermeasures can often be cumbersome to use with populations prone to syncopal episodes. Identifying the mechanisms of inter-individual differences in orthostatic intolerance during heat stress has proven elusive, but could provide greater insights into the development of novel and personalized countermeasures for maintaining or improving orthostatic tolerance during heat stress. This development will be especially impactful in occupational settings and clinical situations that present with orthostatic intolerance and/or central hypovolemia. Such investigations should be considered of vital importance given the impending increased incidence of heat events, and associated cardiovascular challenges that are predicted to occur with the ensuing changes in climate.

Keywords: Orthostasis, cardiovascular control, sympathetic nerve activity, hyperthermia, cutaneous blood flow

Introduction

Global temperatures are rising (Easterling et al., 2000b; Meehl et al., 2007) and weather is predicted to become more variable (Easterling et al., 2000a; Easterling et al., 2000b; Folland et al., 2006; Ratcliffe et al., 2006). This greater weather variability is defined by an increased frequency, intensity, and duration of heat events (Easterling et al., 2000a; Easterling et al., 2000b; Folland et al., 2006; Meehl et al., 2004; Ratcliffe et al., 2006). Cardiovascular health is particularly susceptible to environmental heat, such that a large proportion of the morbidity and mortality during heat events is from cardiovascular causes (Anderson et al., 2009; Danet et al., 1999; Huynen et al., 2001; Kaiser et al., 2007; Kenney et al., 2014a; Knowlton et al., 2009; Vandentorren et al., 2006). Importantly, 2014 was the hottest year on record (Organization, 2015), and hence environmental heat is not only a problem of the future. It is clear, therefore, that currently, and to a larger extent in the forthcoming years, environmental heat poses a significant challenge to the cardiovascular system and health.

When the rate of body heat loss is exceeded by the rate of environmental or internal heat gain, heat stress ensues, which is characterized by elevations in both skin and internal temperatures. Notably, elevations in internal temperature of as little as $\sim 3^{\circ}\text{C}$ above 'normothermia' (i.e., $\sim 37^{\circ}\text{C}$) severely strain physiological systems and can even lead to death (Bouchama et al., 2002). Prevailing evidence suggests that heat loss is primarily controlled by skin sympathetic nerves innervating skin blood vessels and eccrine sweat glands (Hagbarth et al., 1972; Low et al., 2011; Normell et al., 1974), although the precise mechanisms remain unclear (Kellogg, 2006). Heat stress induces cutaneous vasodilation, which allows for increases in skin blood flow of 5-7 L/min (Rowell, 1974), reducing systemic vascular resistance (Rowell et al., 1969). Heat stress also induces sweating, which can result in a sweat rate of upwards to 3 L/hr (Armstrong et al., 1986), reducing circulating fluid volume (Mack et al., 2011). To regulate blood pressure, cardiac output must increase proportionately (Rowell et al., 1969). This is made possible through elevations in heart rate (Rowell, 1974) and cardiac contractility (Brothers et al., 2009a; Bundgaard-Nielsen et al., 2010; Lucas et al., 2015; Nelson et al., 2011a; Stöhr et al., 2011; Wilson et al., 2009a), as well as a redistribution of blood flow and volume away from non-cutaneous regions (e.g., splanchnic and renal vascular beds) (Crandall et al., 2008; Minson et al., 1998; Rowell et al., 1968; Rowell et al., 1971b). These responses are also largely mediated via the sympathetic nervous system (Rowell, 1990), as evidenced by increases in plasma

catecholamine concentrations (Gagnon et al., 2015b; Niimi et al., 1997) and muscle sympathetic nerve activity (Cui et al., 2010; Cui et al., 2002; Gagnon et al., 2015b; Low et al., 2011; Niimi et al., 1997), which increase in proportion to the magnitude of heat stress. During most instances, these responses are sufficiently robust to ensure reductions in blood pressure are minimal (only on the order of 5-10 mmHg) (Crandall et al., 2014; Rowell, 1974). That said, when heat stress is overlayed with an additional challenge to blood pressure, such as orthostasis, blood pressure regulation can become compromised.

The purpose of this review is to provide a concise overview of the physiological mechanisms by which heat stress challenges orthostatic tolerance. We will also review the current evidence regarding inter-individual differences in orthostatic tolerance during heat stress, as well as introduce proven and potential countermeasures that may be used to promote orthostatic tolerance during heat stress. In the context of this review, 'heat stress' refers to the whole-body, passive (i.e., resting) state. Notably, this does not infer that passive heat stress data cannot be applied to the active (i.e., exercising) state. For instance, the orthostatic responses to passive and active heat stress are virtually indistinguishable when skin temperatures are similar (Pearson et al., 2014). During passive heat stress skin temperatures will be profoundly elevated (37-40°C). The magnitude of the increase in internal body temperature will vary between the studies discussed, although it will usually be between 0.7-1.5°C. In all instances, internal body temperature has been measured in the intestines (e.g., via ingestible temperature capsule), rectum, esophagus, mouth, or pulmonary artery. Because of the loss of body water due to sweating, heat stress and dehydration are intimately linked. However, this review will focus primarily on heat stress, although it should be noted that dehydration is an independent modulator of orthostatic tolerance, and has been identified to be an additive factor with heat stress in reducing orthostatic tolerance (Lucas et al., 2013a; Schlader et al., 2015).

Heat stress impairs orthostatic tolerance

Orthostasis results in central hypovolemia, which occurs as a result of blood pooling in the legs due to gravity. To maintain blood pressure during orthostasis, a challenge that reduces ventricular filling and thus stroke volume, a number of cardiovascular adjustments, largely mediated by baroreflexes and the sympathetic nervous system, must transpire to maintain cardiac output (Convertino, 2014; Esler, 2010; Fu et al., 2014; Mano et al., 2003). Such adjustments include elevations in heart rate, cardiac contractility, and vascular

resistance. If these adjustments are insufficient or if the required adjustments exceed the capacity to modulate these variables, cardiovascular decompensation and rapid reductions in blood pressure occur. If this compromises cerebral perfusion, then syncope ensues if the central hypovolemic stimulus is not removed. The ability to withstand a given central hypovolemic insult is experimentally referred to as orthostatic tolerance even if there is no gravity or postural challenge. This can be safely evaluated in humans by inducing central hypovolemia with perturbations such as lower body negative pressure (LBNP) to the point of pre-syncope. Pre-syncope is identified by the onset of syncopal signs and symptoms, which include feeling faint, sustained nausea, rapid and progressive decreases in blood pressure resulting in sustained systolic blood pressure being <80 mmHg and/or relative bradycardia accompanied by a narrowing of pulse pressure. Experimentally, when pre-syncope occurs, the central hypovolemic stimulus is immediately terminated and the syncopal signs and symptoms disappear.

Heat stress profoundly and unanimously reduces orthostatic tolerance. This is portrayed in Figure 1, which presents data from the database out of the Thermal and Vascular Physiology Laboratory in Dallas, TX, USA, which contains a total of 184 observations in which subjects underwent progressive central hypovolemia to pre-syncope via LBNP. Subjects were either heat stressed ($1.4 \pm 0.2^{\circ}\text{C}$ increase in internal temperature) or normothermic (control condition). Orthostatic tolerance was quantified via the cumulative stress index, which is calculated by summing the product of the level of LBNP and the time at each level of LBNP across the trial until pre-syncope (i.e., 20 mmHg x 3 min + 30 mmHg x 3 min, etc.) (Levine et al., 1994). Figure 1 demonstrates a left-ward shift in the Kaplan-Meier survival curve, indicating that orthostatic tolerance during progressive LBNP is impaired during heat stress (Figure 1).

Heat stress induced orthostatic intolerance is not a recent finding. Observations dating to 1949 noted reductions in orthostatic tolerance during head-up tilt following immersion in a hot (40°C) bath (Horvath et al., 1949). Studies from then through to the present have confirmed these findings during head-up tilt (Lind et al., 1968; Shvartz et al., 1970; Wilson et al., 2002b; Yamazaki et al., 2000), while others have consistently demonstrated that orthostatic tolerance is reduced while heat stressed during other central hypovolemic stimuli such as LBNP (Keller et al., 2009; Pearson et al., 2013; Schlader et al., 2014a; Schlader et al., 2014b; Wilson et al., 2006), centrifugation (Nunneley et al., 1979), and linear acceleration (Allan et al., 1972). Given the integrative nature of the cardiovascular

responses required to maintain blood pressure during orthostasis, the mechanisms underlying heat stress induced impairments in orthostatic tolerance are multifactorial. These potential mechanisms, which include the control of cardiac output, vascular resistance, venous responses, and the cerebral circulation, are discussed in the following sections.

Mechanisms of orthostatic intolerance during heat stress

Control of cardiac output

During orthostasis, the heart must deliver blood to generate sufficient blood pressure to perfuse the brain and stave off syncope. While this appears to be a simple engineering task, the physiological responses to heat stress place the heart at some distinct disadvantages to appropriately respond to the additional stress of orthostasis. As a result, producing the necessary cardiac output to compensate for both heat and orthostatic stress is physiologically challenging. We would like to emphasize using the term *necessary* to describe the cardiac output requirements under combined heat and orthostatic stress, since the cardiac output required under these combined stressors may not appear aberrantly low to the clinician, but is in fact inadequate for the conditions. Highlighting this concept, cardiac output at pre-syncope during heat stress can be much higher than normothermic baseline values (Ganio et al., 2012).

Inadequate cardiac output is a key mechanism by which heat stress alters orthostatic tolerance. For instance, volume expansion increases cardiac output during heat stress and attenuates reductions in cardiac output during central hypovolemia (Bundgaard-Nielsen et al., 2010), and under such circumstances, volume expansion during heat stress restores orthostatic tolerance to normothermic levels (Keller et al., 2009) (Figure 2). Notably, cardiac output can be modulated via alterations in stroke volume and/or heart rate.

Cardiac preload modulates stroke volume and likely affects cardiac output responses during combined heat and orthostatic stress. Due to reductions in systemic vascular resistance and associated increases in blood volume in the cutaneous vasculature, heat stress, alone, decreases central blood volume (Crandall et al., 2012; Crandall et al., 2008), which reduces cardiac preload (Wilson et al., 2009a) and potentially compromises stroke volume. The relationship between cardiac preload and stroke volume is not linear, as reductions in cardiac preload affect stroke volume based, in part, on the magnitude of left ventricular stretch (i.e., the Frank-Starling effect). Isolated heart studies indicate that the

shape of the Frank-Starling curve is not altered within physiological heat stress ranges (Klabunde et al., 2013). Rather, heat stress shifts the operating point of the Frank-Starling curve closer to the steep portion of the curve (Bundgaard-Nielsen et al., 2010; Wilson et al., 2009b). With this arrangement, further decreases in pulmonary capillary wedge pressure (i.e., left ventricular stretch / preload), such as would occur during orthostasis (Levine, 1993), cause more profound decreases in stroke volume when heat stressed compared to when normothermic. Ultimately, this may compromise cardiac output to the point where blood pressure is severely compromised.

Increases in cardiac contractility could help maintain stroke volume during heat stress independent of Frank-Starling effects. This would help promote the maintenance of stroke volume and thus, cardiac output, during combined heat and orthostatic stress, in spite of reductions in cardiac preload. In line with this contention, heat stress increases cardiac contractility (Bundgaard-Nielsen et al., 2010; Crandall et al., 2008; Nelson et al., 2010; Stöhr et al., 2011; Wilson et al., 2009a). Importantly, during combined heat and orthostatic stress cardiac contractility is greater than when compared to heat stress alone (Nelson et al., 2011a). Isolated heart studies indicate that within physiological heat stress ranges, inotropic agonists are not more effective at higher temperatures (Klabunde et al., 2013), suggesting that heat stress does not affect cardiac beta-adrenergic receptor transduction or contractile mechanisms. Thus, the increase in contractility with heat stress, with or without orthostasis, likely occurs via increases in cardiac sympathetic nerve activity, and is perhaps contributed to by cardiac parasympathetic withdrawal (Vandecasteele et al., 1999). This conclusion was recently confirmed in spinal cord injured individuals with limited/absent sympathetic cardiac innervation (Shibasaki et al., 2015). Notably, the extent to which increases in cardiac contractility help to maintain orthostatic tolerance during heat stress remains to be determined.

Finally, from a mechanical pump viewpoint, instead of attempting to maintain pump filling (cardiac preload) or pumping harder (cardiac contractility), the pump could simply cycle more often (i.e., increase heart rate) to increase or maintain (cardiac) output. As described above, heart rate increases during heat stress largely via sympathetic enhancement, but also via parasympathetic withdrawal (Gorman et al., 1984; Jose et al., 1970). During orthostasis, heart rate also increases due primarily to baroreceptor unloading, which occurs in response to drops in blood pressure (Convertino, 2014). During combined heat and orthostatic stress, heart rate increases as blood pressure is reduced,

resulting in greater peak heart rates during these combined stressors relative to orthostasis in the absence of heat stress (Schlader et al., 2014a). However, the magnitude of the increase in heart rate from pre- orthostatic stress is attenuated during heat stress compared to normothermic conditions, which is likely due to higher heart rates while heat stressed prior to orthostasis (Figure 3). These data suggest a sub-additive effect of heat and orthostatic stress on heart rate, wherein the increase in heart rate during orthostasis is attenuated during heat stress. It is notable, that the heart rates achieved during combined heat and orthostatic stress were well below maximal levels for most subjects (averaging ~130 bpm). The reason for this apparent blunted heart rate response remains unknown. Importantly however, such an arrangement may be advantageous given that limiting increases in heart rate may allow appropriate time for cardiac filling, particularly given reduced ventricular filling pressures, which could otherwise become comprised if heart rate were to approach maximal levels.

The primary feedback mechanisms for cardiac pump cycle frequency (heart rate) and strength (contractility) during orthostasis are the baroreflexes. The effect of heat stress on baroreflex function in humans has been extensively reviewed and readers are referred to several excellent reviews on the topic (Crandall, 2008; Crandall et al., 2003; Crandall et al., 2010a; Crandall et al., 2014; Gonzalez-Alonso et al., 2008). In brief, the collective evidence generally indicates that heat stress does not impair baroreflex control of the heart, although there are exceptions. For example, heat stress does not change the maximum gain of the carotid-to-cardiac baroreceptor response despite heart rate being elevated via heat stress (Crandall, 2000; Yamazaki et al., 2000). However, integrated (multiple high and low baroreceptor populations) baroreceptor-to-cardiac responses, using procedures such as a Valsalva maneuver, appear to be impaired with heat stress (Davis et al., 2010; Yamazaki et al., 2003). These results are contradictory and are likely a function of the various tests used to examine aspects of the cardiac-baroreflex arcs (Crandall, 2008).

Control of vascular resistance

During orthostasis, vascular resistance must also increase to preserve blood pressure. From an engineering perspective, this task could be more challenging than the control of the heart (pump) since there are competing controls in the vasculature (tubes) during heat stress – i.e., blood pressure regulation vs. heat dissipation (Kenney et al., 2014b). For example, increases in systemic vascular resistance (or reductions in systemic vascular

conductance) are minimal during combined heat and orthostatic stress despite profound reductions in blood pressure (Ganio et al., 2012) (Figure 4). Thus, another mechanism by which heat stress may impair orthostatic tolerance is via altered control of vascular resistance. There are three potential explanations for these alterations: 1) heat stress attenuates increases in cutaneous vascular resistance during orthostasis when cutaneous beds are vasodilated due to heat stress (i.e., a sympatholytic-type effect); 2) non-cutaneous vascular beds that are already experiencing a degree of heat stress induced sympathetic vasoconstriction may not be capable of further vasoconstriction during a subsequent orthostatic challenge; and/or 3) baroreflexes governing vascular control during orthostatic stress may be altered by heat stress.

Crandall et al. (2010b) examined the cutaneous vascular responses to combined heat and orthostatic stress and identified that cutaneous vascular resistance increased only a minor extent leading up to pre-syncope. Given the large reserve of blood contained within the cutaneous vasculature during heat stress (Rowell, 1974), these data suggest that insufficient cutaneous vasoconstriction is likely a major contributor to impaired orthostatic tolerance during heat stress. There are three potential reasons for this lack of responsiveness. First, the cutaneous vasculature during heat stress is not as responsive to a given quanta of sympathetic neurotransmitter (Wilson et al., 2002a), which is likely due to nitric oxide mechanisms (Durand et al., 2005; Hodges et al., 2007; Low et al., 2007; Shibasaki et al., 2007; Shibasaki et al., 2008). Second, there may be less withdrawal of sympathetic vasodilator activity and/or less of an increase in sympathetic vasoconstrictor activity to the skin during orthostasis (Cui et al., 2004b; Shibasaki et al., 2006; Wilson et al., 2001; Wilson et al., 2005). And third, heat stress impairs venous-arteriolar interactions (see Veno-Arteriolar Response section below).

Both heat and orthostatic stress increase sympathetic vasoconstrictor outflow to the muscle, splanchnic, and renal vasculatures. Thus, it is possible that when stresses are combined, it may be difficult to further increase neural outflow and/or further vasoconstrict to that neural signal. Minson et al. (1999) investigated this hypothesis and identified comparable increase in both splanchnic and renal vascular resistance during orthostasis between heat stress and normothermic conditions. Notably however, the level of heating was relatively low (internal temperature increased $\sim 0.5^{\circ}\text{C}$). These data indicate that both splanchnic and renal vasoconstrictor responses to orthostasis may not be impeded during heat stress. Furthermore, muscle blood flow is either unchanged (Heinonen et al., 2011) or

modestly increased (Pearson et al., 2011) during heat stress, while muscle α -adrenergic vasoconstrictor responsiveness is not attenuated by local muscle heating (Keller et al., 2010). Such findings highlight a potentially paradoxical disconnect between sympathetic nerve activity and vasoconstriction in the muscle vasculature. However, it may be that sympathetic vasoconstrictor neural activity to the muscle is effectively putting a 'brake' on heat stress induced reductions in vascular resistance that would otherwise compromise blood pressure. Given such an arrangement, it may be that the extent by which increases in muscle vascular resistance can be sympathetically elevated contributes to orthostatic tolerance during heat stress. In support of this, Cui et al. (2011) identified that subjects with the greatest increase in muscle sympathetic nerve activity during orthostasis under heat stress had better orthostatic tolerance (Figure 5). Thus, an augmented sympathetic response to the muscle may be a strategy to compensate, in part, for other vascular beds that appear to be less influence by orthostasis and subsequent hypotension (e.g., the cutaneous vasculature).

Similar to the aforementioned control of the heart, the manner in which vascular resistance is modulated during orthostasis is largely via baroreflex mechanisms. Thus, any heat stress induced alterations in vascular resistance during orthostasis could be contributed to, or driven by, alterations in baroreflex control of the vasculature. Notably however, baroreflex control of vascular resistance data are somewhat conflicting. For instance, heat stress inhibits the carotid-to-vascular baroreflex (Crandall, 2000), suggesting a greater potential for reductions in blood pressure during orthostasis when heat stressed. That said, the sensitivity of baroreflex modulation of muscle sympathetic nerve activity either is not altered (Cui et al., 2002) or is, in fact, improved (Keller et al., 2006) during heat stress. Interestingly, both electrical stimulation of the carotid sinus nerve (Wallin et al., 1975) and unloading of the cardiopulmonary and carotid baroreceptors during both normothermia and heat stress (Crandall et al., 1996) has no effect on the cutaneous circulation. This highlights a potential baroreceptor mediated mechanism by which cutaneous vascular resistance is largely unaffected by orthostasis when heat stressed (Crandall et al., 2010b). Importantly, during normothermia, orthostasis increases the sensitivity of the baroreflex to modulate vascular resistance (Fu et al., 2006; Schwartz et al., 2012), and this appears to be maintained, or even accentuated, during heat stress (Cui et al., 2004a). Thus, despite that baroreflex modulation appears to have minimal influence

on the cutaneous vasculature, baroreflex modulation of the muscle vascular beds (e.g., MSNA responses) may be improved during combined heat and orthostatic stress.

Venous responses

As a consequence of heat stress induced decreases in cutaneous vascular resistance, cutaneous venous volume must also increase. The mechanisms by which this occurs are likely two fold. The first is associated with the Krogh model that describes changes in blood volume in the compliant venous bed associated with changes in vascular resistance in the upstream arteriolar bed (Krogh, 1912; Rowell, 1983). Specifically, as vascular resistance in the cutaneous arterioles is reduced with heat stress, the pressure in the downstream capillary and venous bed is elevated. Due to the highly compliant nature of the venous bed, this elevation in cutaneous venous pressure results in a large increase in venous volume, which, in turn, reduces the transit time for the blood to pass through the cutaneous vasculature, facilitating the transfer of heat from the skin to the environment (Rowell, 1983; Rowell, 1986b). Conversely, during conditions of increased cutaneous vascular resistance (i.e., skin cooling), the pressure in the cutaneous venous system is reduced and blood is displaced from the cutaneous bed centrally. Importantly, therefore, based upon this Krogh model the lack of increases in cutaneous vascular resistance during orthostasis when heat stressed likely contributes to the lack of mobilization of blood out of the expanded cutaneous venous compartment into the central vasculature, which would otherwise serve to protect against orthostatic hypotension.

The second potential mechanism leading to increased cutaneous venous volume during heat stress is related to the direct and indirect effects of heat on venous tone. Although not consistently observed, it is generally accepted that high skin temperatures increase the compliant nature of the cutaneous venous bed and attenuates venoconstriction (sympatholytic effect), resulting in a greater capacitance at a given pressure (Greenfield et al., 1956; Henry et al., 1949; Rowell, 1986a; Rowell et al., 1971a; Vanhoutte et al., 1970; Webb-Peploe, 1969; Webb-Peploe et al., 1968a; Webb-Peploe et al., 1968b; Zitnik et al., 1971). This likely contributes to the greater reductions in central blood volume during orthostasis while heat stressed (Crandall et al., 2008). Consistent with this mechanism, Henry and Gauer (1950) showed a more rapid increase in foot venous pressure during orthostasis when the limb was heated relative when it was normothermic. Furthermore, when that limb was cooled the increase in foot venous pressure was attenuated by ~25%

during orthostasis. These findings were later corroborated by those showing more rapid increases in calf volume during orthostasis while heat stressed relative to when normothermic (Yamazaki et al., 2002).

Veno-arteriolar response

Congestion of the venous system and subsequent increases in venous pressure, as occurs during orthostasis, causes vasoconstriction upstream to the site of congestion (Andersen et al., 1986; Henriksen et al., 1973; Skagen et al., 1982a; Skagen et al., 1982b). The mechanism(s) by which this response occurs, termed the veno-arteriolar response, is not entirely understood, although it is likely of local neural origin (Crandall et al., 2002; Snyder et al., 2012; Vissing et al., 1997). Under normothermic conditions this veno-arteriolar response is responsible for approximately 45% of the increase in systemic vascular resistance during orthostasis (Henriksen, 1977; Henriksen et al., 1977). Given the importance of increasing systemic vascular resistance during an orthostatic challenge, coupled with findings of inadequate increases in systemic vascular resistance during such a challenge while heat stressed (Ganio et al., 2012) (Figure 4), it may be that heat stress compromises the veno-arteriolar response during venous congestion. This hypothesis was evaluated by Brothers et al. (2009c) and Yamazaki et al. (2006) who showed that heat stress attenuates the magnitude of cutaneous vasoconstriction when the veno-arteriolar response was engaged via limb dependency, and subsequent increases in venous pressure. Notably, the mechanism by which heat stress exerts this effect is unknown, but may be related to altered pressure sensing in the cutaneous venous circulation and/or altered vasoconstrictor responsiveness upstream to the pressure signal. Nevertheless, an attenuated veno-arteriolar response during venous congestion associated with orthostasis while heat stressed likely tempers increases in cutaneous vascular resistance that otherwise would be beneficial in maintaining orthostatic tolerance.

Cerebral vasculature

Despite its small mass, the brain consumes nearly 20% of basal oxygen consumption and thus has high oxygen and substrate delivery needs. Insufficient cerebral perfusion, and thus oxygen delivery, is the primary mechanism for loss of consciousness during central hypovolemia (Meendering et al., 2005; Van Lieshout et al., 2003). It is noteworthy that passive heat stress itself reduces cerebral perfusion (Bain et al., 2013; Brothers et al.,

2009b; Fan et al., 2008; Fujii et al., 2008; Lucas et al., 2010; Lucas et al., 2008; Nelson et al., 2011b; Ogoh et al., 2013; Ogoh et al., 2014; Ross et al., 2012; Schlader et al., 2013a; Wilson et al., 2006; Wilson et al., 2002b); see the following citations for comprehensive reviews on this topic (Bain et al., 2015; Crandall et al., 2014). After a threshold is achieved, the magnitude of the reduction in cerebral perfusion is related to the severity of the heat stress (Bain et al., 2015). For example, during mild to moderate heating, when internal temperature increases between ~0.5 and 1.2°C, cerebral perfusion either does not change or only modestly decreases (Low et al., 2009; Lucas et al., 2008; Schlader et al., 2013a; Wilson et al., 2006; Wilson et al., 2002b). However, further heating results in progressive reductions in cerebral perfusion, such that 20-30% reductions in cerebral perfusion have been noted when internal temperature is elevated greater than 1.5°C (Fan et al., 2008; Fujii et al., 2008; Lee et al., 2013; Nelson et al., 2011b; Ross et al., 2012). The mechanisms responsible for these reductions in cerebral perfusion can be attributed to three factors: 1) Reductions in mean arterial pressure associated with heat stress may reduce cerebral perfusion pressure, which could reduce cerebral blood flow (Bain et al., 2013; Brothers et al., 2009b; Fan et al., 2008; Lee et al., 2013; Low et al., 2008; Lucas et al., 2008; Lucas et al., 2013b; Nelson et al., 2011b; Ogoh et al., 2013; Ross et al., 2012; Wilson et al., 2006). An argument against this however, is that cerebral autoregulation [i.e., the capacity of the cerebral circulation to offset changes in perfusion pressure by intrinsic adjustments in cerebrovascular resistance (Paulson et al., 1989)], is largely unaffected by heat stress (Brothers et al., 2009d; Low et al., 2009). 2) Reductions in arterial carbon dioxide tension associated with heat-induced hyperventilation lead to cerebrovascular vasoconstriction (Bain et al., 2013; Brothers et al., 2009b; Fujii et al., 2008; Low et al., 2008; Nelson et al., 2011b; Ross et al., 2012). And 3) increases in cerebral sympathetic stimulation during heat stress may induce cerebrovascular vasoconstriction (Brothers et al., 2009b).

Regardless of the mechanism, a reduction in cerebral perfusion by upwards to 30% during heat stress will reduce the range by which cerebral perfusion could subsequently decrease during an orthostatic challenge prior to syncope. This point is supported by findings showing lower levels of cerebral perfusion for a given magnitude of orthostatic stress when heat stressed (Lucas et al., 2008; Lucas et al., 2013a; Pearson et al., 2013; Wilson et al., 2006), with cerebral perfusion at pre-syncope being similar between normothermic and heat stressed conditions (Lucas et al., 2013a; Pearson et al., 2013). Interestingly however, the magnitude of reductions in cerebral perfusion (as measured via

middle cerebral artery blood flow velocity) to heat stress itself are not related to the subsequent reductions in orthostatic tolerance relative to when normothermic (Lee et al., 2013). Furthermore, Lucas et al. (2013b) identified a disconnect between middle cerebral artery blood flow velocity and orthostatic tolerance during heat stress, such that administering 5% carbon dioxide to the inspire during orthostatic stress, which increased cerebral blood flow back to pre-heat stress levels, did not improve orthostatic tolerance. These findings suggest that heat-induced reductions in cerebral perfusion may not be responsible for reduced orthostatic tolerance during heat stress. Alternatively however, it may be that reductions in cerebral perfusion in the regions perfused by the middle cerebral artery are not responsible for symptoms associated with pre-syncope. This speculation is corroborated by data indicating differential cerebral blood flow regulation in the anterior compared to the posterior circulations (Sato et al., 2012), but is contradicted by studies demonstrating relationships between symptoms of pre-syncope and corresponding reductions in middle cerebral artery blood velocity (Albina et al., 2004; Hermosillo et al., 2006). Furthermore, together with normothermic data (Lewis et al., 2014), these findings may also suggest that cardiovascular adjustments may contribute more to orthostatic tolerance than cerebral perfusion per se, the latter of which may be due to compensatory increases in cerebral oxygen extraction (Bain et al., 2014; Bain et al., 2015).

Inter-individual differences in orthostatic tolerance during heat stress

Orthostatic tolerance varies between individuals during normothermia (Convertino et al., 2012; Convertino et al., 2000a; Convertino et al., 2000b; Greenleaf et al., 2000; Hinojosa-Laborde et al., 2011; Levine et al., 1994; Rickards et al., 2011). As a result, there is great interest in understanding inter-individual differences in orthostatic tolerance, with the hope of developing strategies to improve such tolerance. Factors associated with greater tolerance during orthostasis when normothermic are numerous and include an augmented vasoactive hormone response (Convertino et al., 2000b; Greenleaf et al., 2000), higher increases in vascular resistance (Convertino et al., 2012; Convertino et al., 2000b; Sather et al., 1986), greater increases in heart rate (Convertino et al., 2012; Convertino et al., 2000a; Sather et al., 1986), enhanced protection of central blood volume and cerebral perfusion (Levine et al., 1994), and augmented oscillations in blood pressure and cerebral blood flow (Rickards et al., 2011).

Despite that heat stress unanimously reduces orthostatic tolerance, inter-individual differences in tolerance persist (Brothers et al., 2011; Lee et al., 2014; Lee et al., 2013; Schlader et al., 2014a). Unfortunately, compared to the normothermic state, the identification of factors determining inter-individual differences in orthostatic tolerance during heat stress has proven relatively elusive. For instance, heat stress induced reductions in central venous pressure (Brothers et al., 2011), reductions in cerebral perfusion (Lee et al., 2013), the vasoactive hormone response (Lee et al., 2013), cerebrovascular reactivity to carbon dioxide tension (Lee et al., 2014), differences in aerobic fitness (Lee et al., 2013), and the increase in heart rate during orthostasis (Schlader et al., 2014a) have all proven unable to explain inter-individual differences in orthostatic tolerance during heat stress. To date, two factors have been identified that explain at least a portion of the inter-individual variation in heat stressed orthostatic tolerance. First, in a relatively large cohort of observations (n=60), Schlader and Crandall (2014a) identified that normothermic orthostatic tolerance partially predicts heat stressed orthostatic tolerance, although it explains only ~38% of the variance. Second, Cui et al. (2011) identified that those individuals with the greatest increase in muscle sympathetic nerve activity during orthostasis while heat stressed also had the highest orthostatic tolerance under these conditions (Figure 5). Clearly, further research is required.

Potential differences in orthostatic tolerance during heat stress may also exist between males and females or between younger and older adults. For instance, orthostatic hypotension and orthostatic intolerance are particularly prevalent in older adults (Rutan et al., 1992). To our knowledge, no studies have systematically quantified orthostatic tolerance during heat stress in older adults. During heat stress, older adults have attenuated increases cardiac output (Greaney et al., 2015; Minson et al., 1998) and appear utilize different strategies during combined heat and orthostatic stress, relying more on increases in renal and splanchnic vascular resistance, rather than increases in limb vascular resistance (Minson et al., 1999). Older adults also exhibit greater reductions in cerebral perfusion and slower corrections in blood pressure during orthostasis while heat stressed (Lucas et al., 2008). This maybe due to age induced alterations in baroreflex function (Monahan, 2007), which may also be present during heat and orthostatic stress (Greaney et al., 2015; Shiraki et al., 1987). By contrast, the increase in muscle sympathetic nerve activity during mild central hypovolemia while heat stressed is not affected by aging (Gagnon et al., 2015a), which may ultimately explain why older adults are generally

asymptomatic throughout combined heat and orthostatic stress (Lucas et al., 2008). Collectively therefore, older adults may or may not have increased incidences orthostatic intolerance during heat stress compared to a younger cohort.

Females have lower orthostatic tolerance than males during normothermia (Convertino, 1998; Montgomery et al., 1977; Waters et al., 2002), which is also true during heat stress (Meendering et al., 2005). These observations are likely due to differential reliance on neural and hemodynamic mechanisms to maintain blood pressure in females compared to males (Hart et al., 2012) and/or differences in cardiac left ventricle size and alterations in Frank-Starling relations (Fu et al., 2004). Importantly, no studies have examined if sex modifies the magnitude by which heat stress reduces orthostatic tolerance. Clearly, more formal research investigating sex differences is required to address these questions.

Countermeasures for improving orthostatic tolerance during heat stress

Countermeasures for improving orthostatic tolerance during heat stress generally aim to reverse the central hypovolemic stress by augmenting central blood volume either directly (e.g., via volume expansion) or by increasing vascular resistance during orthostasis. For instance, in the supine position skin surface cooling, which is insufficient to change internal temperature, elicits peripheral (e.g., skin) and visceral (e.g., splanchnic, renal) vasoconstriction and increases blood pressure (Cui et al., 2005; Wilson et al., 2007a). During orthostasis while normothermic, skin surface cooling increases central venous pressure and pulmonary capillary wedge pressure (Cui et al., 2005; Wilson et al., 2007b), reduces the magnitude of venous pooling (Durand et al., 2004), and increases blood pressure (Durand et al., 2004), all of which result in smaller reductions in stroke volume (Cui et al., 2005) and cerebral perfusion (Durand et al., 2004). As a result, normothermic orthostatic tolerance is improved by skin surface cooling (Durand et al., 2004). These findings have also been extended to heat stress, whereby rapid skin surface cooling increases central venous pressure, and reduces heart rate and cardiac output despite high prevailing internal temperatures (Rowell et al., 1969). Thus, heat stressed orthostatic tolerance is improved with skin surface cooling (Wilson et al., 2002b), which occurs, at least partially, via increased peripheral vascular resistance, increased ventricular filling pressures (Wilson et al., 2007b), and better maintenance of cerebral perfusion during orthostasis (Wilson et al., 2002b).

Similar to skin surface cooling, acute volume expansion reverses heat stress induced reductions in orthostatic tolerance (Figure 2) (Keller et al., 2009). As mentioned above, this re-loading of the central vasculature (Bundgaard-Nielsen et al., 2010; Crandall et al., 2008) augments cardiac output and stroke volume (Brothers et al., 2014), which better maintains blood pressure during a given orthostatic stimulus (Keller et al., 2009; Schlader et al., 2013b). Thus, reductions in cerebral perfusion are attenuated during orthostasis under such heat stressed and volume loaded circumstances (Schlader et al., 2013b).

Importantly, not all potential countermeasures are effective in alleviating reductions in orthostatic tolerance during heat stress. For instance, as described above, reversal of heat stress induced reductions in cerebral perfusion, via the introduction of carbon dioxide into the inspire, has no effect on orthostatic tolerance (Lucas et al., 2013b). These findings suggest that interventions aimed specifically at the cerebral circulation, in the absence of addressing systemic cardiovascular factors, may not be a viable countermeasure for ensuring orthostatic tolerance during heat stress. Notably however, this hypothesis should be tested further using different methods, as 5% inspired carbon dioxide may have also exerted systemic effects that contributed to the impaired orthostatic tolerance.

Other countermeasures that are commonly employed to treat orthostatic intolerance in clinical settings may also be effective during heat stress. These include drinking boluses of water to initiate reflex vasoconstriction (Lu et al., 2003), which occurs via intragastric and intraduodenal transient receptor potential vanilloid 4 channel activation (McHugh et al., 2010), activating the muscle pump via contracting muscles in the legs (e.g., applied muscle tension), or increasing plasma volume via either increased salt intake or drug interventions (e.g., vasopressors or mineralocorticoids) (Figueroa et al., 2010; Wieling et al., 2011). Unfortunately however, the efficacy of these clinical countermeasures during heat stress remains uncertain, and it cannot be assumed that these countermeasures will be effective during heat stress. For instance, the cold pressor test, which induces large and robust increases in blood pressure during normothermia, does not elicit as great of increases in blood pressure during heat stress (Cui et al., 2010). Therefore, water drinking, which elicits a moderate increase in blood pressure during normothermia (Lu et al., 2003), may not be as effective under heat stress. However, it may also be that the sensitivity of intragastric and intraduodenal receptor responses are unaffected by heat stress, resulting in similar responses relative to that observed in normothermic individuals. Thus, research

examining the effectiveness of simple and easily implemented orthostatic intolerance countermeasures during heat stress is required.

Conclusion

It is clear that heat stress profoundly and unanimously reduces orthostatic tolerance. The mechanisms underlying these observations are multifactorial and involve interactions between multiple physiological systems. Potential factors include those associated with the arterial and venous arms driving changes in vascular resistance and blood distribution, and the modulation of cardiac output, all of which contribute to the inability to maintain cerebral perfusion during heat and orthostatic stress. A number of countermeasures have been established that aim to either alleviate heat stress induced central hypovolemia and/or improve orthostasis induced increases in peripheral vascular resistance. Unfortunately, these countermeasures are rather cumbersome to employ in clinical populations and acute care occupational (e.g., military, mining) or injury (e.g., hemorrhage) situations in which heat stress and orthostatic stress or central hypovolemia are common. Thus, further research is required to establish the effectiveness of simple, clinical countermeasures for improving orthostatic tolerance during heat stress. Finally, identifying the mechanisms of inter-individual differences in orthostatic intolerance during heat stress has proven relatively elusive, but if understood these mechanisms could promote the development of novel and personalized countermeasures for ensuring orthostatic tolerance during heat stress. Such investigations should be considered of vital importance given global warming and the impending increased incidence of heat events, which could have significant impacts on cardiovascular health.

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1044 **Figures**

1045
1046 **Figure 1:** Orthostatic tolerance during lower body negative pressure, quantified via the
1047 cumulative stress index (see text), is unanimously reduced by passive heat stress sufficient
1048 to increase internal temperature by a mean of ~1.4°C.

1050
1051 **Figure 2:** Heat stress induced orthostatic intolerance during lower body negative pressure,
1052 quantified via the cumulative stress index (see text), is restored by volume expansion via a
1053 dextran solution (mean $\pm$ SD, $n=7$). * different from Control and Dextran ($P<0.05$). Figure
1054 redrawn from Keller et al. (2009), with permission.

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Figure 3: Mean arterial pressure (MAP, top), heart rate (middle), and the change (Δ) in heart rate from Pre- lower body negative pressure (LBNP, bottom) during normothermic and heat stressed LBNP pre- thermal perturbation (Baseline), immediately prior to commencing LBNP (Pre-LBNP), the highest heart rate achieved during the final 2 min of LBNP (i.e., prior to any bradycardia, Peak-LBNP), and immediately prior to LBNP termination (Pre-Syncope) (mean $\pm$ SD, n=60). Despite greater absolute heart rates during heat stress, the increase in heart rate during LBNP is attenuated with heat stress despite greater reductions in arterial pressure. *, indicates different from Normothermia ($P \leq 0.029$);

1065 1, 2, and 3, indicate different from Baseline, Pre-LBNP, and Peak-LBNP, respectively
1066 ($P \leq 0.018$). Figure redrawn from Schlader and Crandall (2014a), with permission.

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Figure 4: Systemic vascular conductance (top), the inverse of vascular resistance, and mean arterial pressure (bottom), during normothermia, passive heat stress, and throughout an orthostatic challenge (i.e., lower body negative pressure) to pre-syncope (100%) while heat stressed (mean $\pm$ SD, n=11). Under heat stressed during orthostasis, despite profound hypotension, systemic vascular conductance was not reduced. Systemic vascular conductance was calculated as the quotient of thermodilution derived cardiac output measurements and mean arterial pressure. * different from Normothermia (P<0.05), † different from 1.2°C increase in internal temperature (P<0.05). Figure redrawn from Ganio et al. (2012), with permission.

1078
 1079 **Figure 5:** Positive correlation between the increase in muscle sympathetic nerve activity
 1080 (MSNA) burst rate during orthostasis (head-up tilt) and orthostatic tolerance (tilt time, i.e.,
 1081 time to pre-syncope) during heat stress. These data indicate that those individuals with
 1082 greatest increases in muscle sympathetic nerve activity during combined heat and
 1083 orthostatic stress possess better orthostatic tolerance. Figure redrawn from Cui et al.
 1084 (2011), with permission.