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Review

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 occuational 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.

Contents

1. 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, 2000b; Folland et al., 2006; Ratcliffe et al., 2006). This

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greater weather variability is defined by an increased frequency, intensity, and duration of heat events (Easterling et al., 2000a, 2000b; Folland et al., 2006; Meehl and Tebaldi, 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 and Bell, 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 ~3 °C above 'normothermia' (i.e., ~37 °C) severely strain physiological systems and can even lead to death (Bouchama and Knochel, 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 and Wallin, 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/h (Armstrong et al., 1986), reducing circulating fluid volume (Mack and Nadel, 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., 2009), 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, 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., 2015; Niimi et al., 1997) and muscle sympathetic nerve activity (Cui et al., 2002, 2010; Gagnon et al., 2015; 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 and Wilson, 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 indistiguishable 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 and 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).

2. 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 and Levine, 2014; Mano and Iwase, 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 Fig. 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 ± 0.2 °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 × 3 min + 30 mmHg × 3 min, etc.) (Levine et al., 1994). Fig. 1 demonstrates a left-

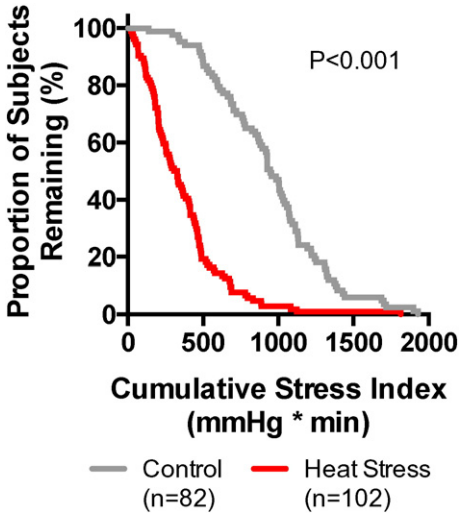

Fig. 1. Orthostatic tolerance during lower body negative pressure, quantified via the cumulative stress index (see text), is unanimously reduced by passive heat stress sufficient to increase internal temperature by a mean of ~1.4 °C.