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AUTONOMIC NERVOUS SYSTEM FUNCTION FOLLOWING EXERCISE-INDUCED HYPERTHERMIA

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ABSTRACT

Exercise in the heat is associated with cardiovascular and thermoregulatory disturbances that can persist postexercise. The effect of orthostasis on autonomic nervous system function following exercise-induced hyperthermia (EIH) remains to date unclear. Insight into the mechanisms of control is beneficial to those encountering orthostatic challenges after activity-induced hyperthermia.

We evaluated the short-term postexercise cardiovascular and thermoregulatory responses to repeated orthostatic challenges performed in a hyperthermic state and the effects of EIH on autonomic nervous system function during repeated orthostatic challenges in the early and late-stages of recovery.

We conclude that following EIH, the cardiovascular system maintained arterial pressure and cardiac output during repeated 70° head-up tilts. Nonthermal baroreceptor control predominates over thermal control of cutaneous vascular conductance during postural challenges following EIH, but no effect was observed in local sweat rate. The short-term reductions in baroreceptor sensitivity and heart rate variability following EIH were re-established following a 24-h recovery period.

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Finally, I would like to dedicate this thesis to my late mother, Maria. You are missed everyday but your presence is felt always.

ABSTRACT

Background: Exercise in the heat is associated with significant cardiovascular (hypotension) and thermoregulatory (attenuated heat loss mechanisms) that can persist for a prolonged period postexercise. The effect of orthostasis on autonomic nervous system (ANS) function during the short and long-term postexercise period after hyperthermia remains to date unclear. Greater insight into the underlying mechanisms of control is beneficial to those encountering orthostatic challenges after or during intermittent activity-induced hyperthermia such as military (pilots) and civilian (firefighters) personnel, industrial workers (miners), astronauts, and athletes.

Objectives: *Article I.* To evaluate the short-term postexercise cardiovascular and thermoregulatory responses to repeated orthostatic challenges performed in a state of hyperthermia (rectal temperature $\geq$ 39.5°C); and, *Article II.* To evaluate the effects of exercise-induced hyperthermia on ANS function during a repeated orthostatic challenge in the early- (<80 min) and late-stages (24 and 48-h) of recovery.

Methods: *Article I & II.* Eight male subjects performed a repeated orthostatic challenge under a non-exercise/non-heat stress state (NH), following exercise-induced heat-stress (EIH) and at 24 and 48-h postexercise. On each day subjects remained supine for 30 min in a thermoneutral environment (22°C) and were subsequently exposed to three successive 6-min 70° head-up tilts (HUT1, HUT2 and HUT3), each separated by 10-min supine resting. During EIH, subjects were rendered hyperthermic (rectal temperature $\geq$39.5°C) by exercise in the heat (42°C) and were then transferred to a thermoneutral environment.

Results: *Article I.* ΔMAP was greater in HUT3 during EIH (17.5±2.7 mmHg) versus NH (7.4±3.6 mmHg) ($p < 0.05$), paralleled by a greater ΔTPR during EIH (5.6±0.8 mmHg·L^{-1}·min) ($p < 0.05$). BRS remained depressed throughout each HUT cycle in EIH compared to NH ($p < 0.05$). A transient reduction in ΔCVC_{max} was observed with each HUT ($p < 0.05$) whereas no differences were observed in ΔLSR.
Article II. Reductions in BRS and HRV were observed during EIH compared to NH throughout the short-term recovery period (<80 min) ($p \leq 0.05$), but were restored following 24-h of recovery. Greater ΔMAP was observed following 24-h of recovery compared to NH ($p \leq 0.05$).

Conclusions: *Article I.* Following exercise-induced hyperthermia MAP is maintained during repeated orthostatic stress likely due to increases in TPR paralleled by significant reductions in BRS. While nonthermal baroreceptor control predominates over thermal control of CVC during repeated orthostatic challenges following EIH, no effect was observed in local sweat rate.
Article II. Exercise-induced hyperthermia causes a short-term reduction in BRS and HRV which is further exacerbated by an orthostatic challenge. Normal baseline BRS and HRV response is re-established following a 24-h recovery period.

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PART ONE:

EMPIRICAL AND THEORETICAL CONSIDERATIONS

CHAPTER 1
INTRODUCTION

1.0 Background

Exercise in the heat is associated with significant cardiovascular (hypotension) and thermoregulatory (attenuated heat loss mechanisms) that can persist for a prolonged period postexercise (Journeay *et al.*, 2007; Kenny *et al.*, 2007; Kenny and Niedre, 2002). Following the completion of exercise, there are profound changes in the mechanisms that regulate and determine mean arterial pressure, which result in hypotension that is both vascular and neural in origin (Halliwill, 2001). This postexercise hypotension is paralleled by thermoregulatory changes such as reductions in skin blood flow (Kenny *et al.*, 2003) and sweating (Kenny *et al.*, 2003) despite sustained elevations in core temperature (Kenny *et al.*, 2006). The magnitude of the response is influenced by the level of exercise intensity (Kenny *et al.*, 2006) and level of hyperthermia (Gagnon *et al.*, 2008).

There is increasing evidence to support the theory that nonthermal baroreceptor afferent stimuli associated with postexercise hypotension are responsible for the efferent modulation of autonomic thermoeffector activity (Journeay *et al.*, 2004; Kenny *et al.*, 2006; McInnis *et al.*, 2006). Previous studies have reported that attenuating the baroreceptor unloading effect of exercise recovery in the early stages of recovery by the application of positive pressure to the lower limbs (+45mmHg) (Jackson & Kenny, 2003; Journeay *et al.*, 2004), head-down tilt (McInnis *et al.*, 2006), supine recovery (Kenny *et al.*, 2008), or active/passive cycling (Gagnon *et al.*, 2008), the postexercise attenuation of skin blood flow and sweating are reversed and give rise to a decrease in the time for the return of core temperature to resting values. Taken together, these findings demonstrate a

physiological link between the observed postexercise cardiovascular changes and altered thermoregulatory control. However, cardiovascular and thermoregulatory control during repeated orthostatic challenges following exercise-induced hyperthermia (defined as a rectal temperature of 39.5°C) has not previously been examined in conjunction with direct measures of autonomic nervous system (ANS) function.

Baroreceptors are pressure sensors of the ANS (Samniah *et al.*, 2004) that respond to changes in blood pressure by initiating appropriate cardiovascular responses. Baroreceptor sensitivity (BRS) is defined as the change in heart beat interval per unit change in blood pressure, expressed in $ms \cdot mmHg^{-1}$ (Westerhof *et al.*, 2006). Furthermore, heart rate variability (HRV), the fluctuation of heart rate about the mean heart rate, can be used as a reflection of the cardiorespiratory control system providing information regarding the balance between sympathetic and parasympathetic function of the ANS (Van Ravenswaaij-Arts *et al.*, 1993). Attenuations in HRV have been documented during acute and chronic illness (Goldberger *et al.*, 2002) and aging (Ferrari, 2002; Goldberger *et al.*, 2002). Insight into baroreflex behaviour is of clinical relevance, since an attenuated baroreflex response is a factor gaining use to poorer prognosis for cardiovascular diseases (Skrapari *et al.*, 2007).

Previous studies to date have demonstrated that reductions in BRS and HRV occur during passively-induced mild heat stress (Lee *et al.*, 2003; Crandall *et al.*, 2000; Yamamoto et al., 2007), exercise (Ogoh *et al.*, 2005; Terziotti *et al.*, 2001; Niemela, 2008), recovery from exercise (Terziotti *et al.*, 2001; Niemela, 2008; Parekh and Lee, 2005) and postural stress (Westerhof *et al.*, 2006; Butler *et al.*, 1994). Therefore, postural manipulation can be used to evaluate BRS and HRV under a non-exercise/non-heat stress

and exercise-induced hyperthermia state. During head-up tilt, baroreceptors are unloaded due to blood pooling in the lower limbs. The greater the angle in the head-up tilt position, the greater the reduction in BRS and HRV (Westerhof *et al.*, 2006; Butler *et al.*, 1994). In the upright posture, the greatest portion of blood volume is located below heart level and as a result an increase in sympathetic drive (heart rate, total peripheral resistance, and cardiac output) helps maintain normal blood pressure. However, when passively-induced whole-body heat stress is combined with the increased cardiovascular demands of upright posture, the heat-induced elevations in skin blood flow and sweat rate, along with venous pooling and a decrease in blood pressure produce significant reductions in venous return and stroke volume (Cui *et al.*, 2003). The combined effects of heat stress and upright posture make it even more difficult to maintain adequate blood pressure.

It is well known that humans are more susceptible to syncope during orthostasis under hyperthermic conditions compared to cool environmental conditions (Crandall *et al.*, 2000). The reduction in orthostatic tolerance associated with passively-induced mild heat stress (i.e., core temperature = 38.0°C) in humans has been suggested to be primarily a function of impaired baroreflex responsiveness (Cui *et al.*, 2003). Thermal strain is accompanied by high levels of cardiovascular strain and an impairment of blood pressure regulation and/or critical levels of blood flow to the brain and splanchnic tissues (Cheung, 2007). During exercise, cerebral temperature is known to rise in parallel with core temperature (Nybo, 2008). The development of fatigue and subsequently exhaustion coincides with the attainment of a critical core temperature (~40°C) and the thermodynamic response of the brain is of special interest as brain temperature appears to be a dominant factor affecting motor activity (Nybo, 2008). While studies eliciting

hyperthermia via exercise in the heat have generally supported a dominant central impairment of neuromuscular activation (Cheung, 2007), the impact on visceral motor (involuntary) activity of the ANS remains unknown.

Furthermore, it is unclear if postexercise hypotension combined with attenuated heat loss mechanisms of skin blood flow and sweating associated with exercise in the heat can pose prolonged effects on ANS function to orthostatic stress at 24 and 48-h postexercise. Exercise is known to elicit a persistent reduction in mean arterial pressure lasting nearly 2 hours in healthy normotensive individuals and as long as 12 hours in hypertensive patients and is further exacerbated by increasing levels of thermal stress (Halliwill, 2001). While a lack of research exists on the long-term recovery pattern of ANS function, investigators have reported attenuations in HRV (a decreased vagal modulation of the heart) for up to 24-h after exhaustive exercise regimens (Bernardi *et al.*, 1997; Furlan *et al.*, 1993; Hautala *et al.*, 2001).

1.1 Rationale

By employing an exercise paradigm which has previously been shown to elicit a pronounced reduction in arterial blood pressure paralleled by attenuated heat loss responses (i.e., skin blood flow and sweating) we can evaluate short-term cardiovascular and thermoregulatory responses to repeated orthostatic stress during higher levels of thermal stress. Furthermore, both BRS and HRV are known to be reduced during postural stress therefore, postural stress can be used to evaluate ANS function during hyperthermia compared to a non-exercise/non-heat stress condition. By using an

orthostatic challenge as a means to asses the cardiovascular system we eliminate any possible side-effects of drug-induced changes in arterial pressure.

1.2 Purpose:

The following study was conducted to assess the effect of exercise-induced hyperthermia (rectal temperature ≥39.5°C) on cardiovascular and thermoregulatory control during repeated orthostatic stress in the postexercise period. Furthermore, BRS and HRV were used as indicators of ANS function during the short (<80 min) and long-term (24 and 48-h) recovery period following exercise-induced hyperthermia. By evaluating ANS function during the postexercise period, we are able to provide a greater insight into the competing demands (cardiovascular and thermoregulatory) of exercise in the heat and how this ultimately affects long-term recovery.

1.3 Study Objectives:

1) To evaluate the short-term postexercise cardiovascular and thermoregulatory responses to repeated orthostatic challenges performed in an elevated hyperthermic state (rectal temperature ≥ 39.5°C).

2) To determine if severe hyperthermia induced through exercise in the heat can alter ANS function (as measured by BRS and HRV) in the short-term (<80-min) recovery period and if so, to evaluate the long-term residual consequences of altered autonomic nervous system function during repeated orthostatic challenges presented 24 and 48-h postexercise.

1.4 Hypothesis:

We tested the hypothesis that exercise-induced hyperthermia would exacerbate the fall in stroke volume and reduce the magnitude of increase in total peripheral resistance, causing a reduction in arterial blood pressure during repeated orthostatic challenges. Further, we also tested the hypothesis that following exercise-induced hyperthermia, there will be a reduction in cutaneous vascular conductance and local sweat rate during 70° HUT due to the overriding nonthermal baroreceptor modulation of thermal effector activity. We hypothesizesd that severe hyperthermia induced by exercise in the heat will result in alterations in ANS function compared to a non-heat stress condition. Short-term adjustments in BRS and HRV following exercise-induced hyperthermia would not be restored to baseline resting levels by 24-h postexercise but would be re-established after 48-h.

1.5 Relevance

Exercise in the heat is associated with significant cardiovascular and thermoregulatory disturbances that can persist for a prolonged period postexercise. The effect of orthostasis on ANS function during the short and long-term postexercise period after hyperthermia remains to date unclear. Greater insight into the underlying mechanisms of control is advantageous to those encountering orthostatic challenges after or during intermittent activity-induced hyperthermia such as military (pilots) and civilian (firefighters) personnel, industrial workers (miners), astronauts, and athletes.

1.6 Delimitations and Limitations

There was an imposed restriction as to the degree of hyperthermia brought about by exercise. The increase in core temperature was limited to a target rectal temperature of 39.5°C. Subjects recruited for the study were young physically active male adults aged 22 ± 3 yrs. Therefore, the results of this study cannot apply to females, children, the elderly, or to a sedentary populations. It must be noted that by using a tilt table to induce changes in mean arterial pressure the vestibular system may be stimulated however changes in position were performed within 30 sec to limit the activation of vestibular reflexes.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Thermoregulation

2.1.1 Human Thermoregulation

Humans are homeotherms therefore, under normal circumstances body temperature is maintained within certain reasonably narrow limits (Schonbaum & Lomax, 1990). Temperature is a reflection of the heat content of a body and is proportional to the average kinetic energy of an atom of gas in random motion. Therefore, temperature indicates the relative speed of physical and chemical processes (Schonbaum & Lomax, 1990). One of the ways in which the body gains heat is through muscular activity. At the onset of exercise, heat production rises abruptly and body temperature rises until heat loss matches the increased heat production so that there is a sustained hyperthermia (Schonbaum & Lomax, 1990). The increases in heat production that occur through exercise are offset through heat loss from the body by conduction, radiation, and evaporation. Body heat content is constant when the rate of heat production (thermogenesis) is equal to the rate of heat loss (thermolysis). Core temperature rises if heat gain exceeds heat loss and is measured most commonly in the oesophagus, the auditory canal, and the rectum.

During thermoregulation the body transfers internal heat away from the body to the external environment (King, 2004). The transfer of heat between the core and periphery is accomplished through conductive and convective blood flow to the skin. During heat stress conditions, when ambient temperature is higher than body temperature, evaporative cooling of the skin provides the major defense against

overheating by maintaining a gradient between the core and the periphery. In this case there is a net heat gain by conduction and radiation. According to the second law of thermodynamics, energy is transferred from a higher temperature to a lower temperature. Therefore, when ambient temperature is greater than body temperature, the body actually gains heat through radiation and conduction. The greatest amount of heat under such heat stress conditions is therefore dissipated from the body through evaporative processes from the skin and respiratory tract. The transfer of heat to the skin during heat stress occurs through increased convective flow through cutaneous vasodilation such that a greater amount of heat is lost to the external environment (King, 2004). Under conditions of elevated internal temperature there is a diversion of arterial blood to the periphery favouring transport of heat energy to the skin surface through increases in cutaneous vasodilation, skin blood flow and sweating. Under equilibrium conditions, the thermal balance of the human body is expressed by the heat balance equation:

$$M\text{-}W = (K + C + R + E_{SK}) + (C_{RES} + E_{RES}) + S$$

M = rate of metabolic heat production
W= rate of mechanical work (effectively = 0)
K= rate of conductive heat loss
C= rate of convective heat loss from the skin
R= rate of radiative heat loss from the skin
E_{SK}= rate of evaporative heat loss from the skin
C_{RES}= rate of convective heat loss from respiration
E_{RES}= rate of evaporative heat loss from the respiration
S= rate of body heat storage (all units $W \cdot m^{-2}$)

2.1.2 Thermal influences on the regulation of body temperature

The main integrating center for thermoregulation is localized in the hypothalamus and includes the heat-loss center (located anteriorly) and the heat-promoting center

(located posteriorly) (Marieb, 2004). The primary thermal mechanism for stimulating heat loss responses is via a hypothalamic negative feedback loop that receives afferent input from the skin (peripheral thermoreceptors) and core (central thermoreceptors) (Journeay *et al.*, 2006; Charkoudian, 2003). An increase in skin and core temperatures signals the preoptic region of the hypothalamus to initiate heat dissipation through increased cutaneous vasodilation, skin blood flow, and sweating (Charkoudian, 2003). The thermoregulatory center is directly influenced by thermal stimuli derived from body core and skin tissue regions. In response to rising core body temperature, the thermal center activates the efferent fibers of the autonomic nervous system to produce cutaneous vasodilation and increases in skin blood flow and sweat rate subsequently leading to a decrease in core temperature (Journeay *et al.*, 2006). These two responses are the principal effectors of temperature regulation in humans (Fig. 1).

2.1.3 Nonthermal influences on the regulation of body temperature

In addition to thermal mechanisms at the level of the hypothalamus, nonthermal factors (Kenny *et al.*, 2003) also effect skin blood flow and sweating responses and ultimately changes in core body temperature. Nonthermal stimuli include the cardiorespiratory control systems (arterial and cardiopulmonary baroreceptors) as well as mechanoreceptors and metaboreceptors of skeletal muscle (i.e., exercise pressor reflex) (Journeay *et al.*, 2006; Raven *et al.*, 2006). These nonthermal stimuli modulate central command activity (i.e. the hypothalamus) where all information from these centers is integrated (Fig. 1) (Journeay *et al.*, 2006).

The cardiorespiratory center receives input from two populations of baroreceptors, namely the arterial and cardiopulmonary baroreceptors. Baroreceptors are pressure sensitive nerve endings in the walls of the atria of the heart, the vena cava, the aortic arch, and the carotid sinus (Marieb, 2004). Baroreceptors function on a negative feedback loop system which operates to attenuate perturbations in blood pressure (Kamijo *et al.*, 2005). The afferent stimuli are directed to the brainstem thereby activating the autonomic nervous system. The vasomotor center is the neural center located in the brain that stimulates vasodilation or vasoconstriction at arterioles and veins depending on the impulse sent from the baroreceptors. If there is a rise in arterial pressure, baroreceptors stretch, causing an increase in afferent neuronal firing. An impulse is sent to inhibit the vasomotor center, resulting in vasodilation of arterioles and veins. A rise in blood pressure stimulates the cardiac accelerator centre and a decline in sympathetic nervous system activity (heart rate, cardiac output, and total peripheral resistance) and an increase in parasympathetic nervous system activity which results in a reduction in blood pressure (Kamijo *et al.*, 2005). In contrast, during reductions in arterial blood pressure, afferent firing is reduced therefore baroreceptors activate the vasomotor center causing an increase in sympathetic nervous system activity (heart rate, cardiac output and total peripheral resistance) and a decline in parasympathetic nervous system activity. The result is vasoconstriction and an increase in blood pressure. The central components governing thermoregulation are located in the hypothalamus and electrical stimulation of the hypothalamus is known to modify the baroreceptor reflex (Crandall *et al.*, 2003). The close integration of thermal and nonthermal mechanisms appear to support the assumption that human baroreceptor reflex responses are modified in heat stress

conditions (Crandall *et al.*, 2003). Previous research has demonstrated that reductions in blood pressure through application of lower body negative pressure and head-up tilt position unloads baroreceptors causing vasoconstriction and therefore reductions in heat loss responses (skin blood flow and sweating) (Jackson & Kenny, 2003; Cui *et al.*, 2004). However, maintenance of blood pressure through application of lower body positive pressure and head-down tilt position loads baroreceptors causing vasodilation leading to increases in heat loss (Jackson & Kenny, 2003; Journeay *et al.*, 2004; McInnis *et al.*, 2006). Sustained elevations in skin blood flow and sweating through baroreceptor loading ultimately lead to decreases in core temperature.

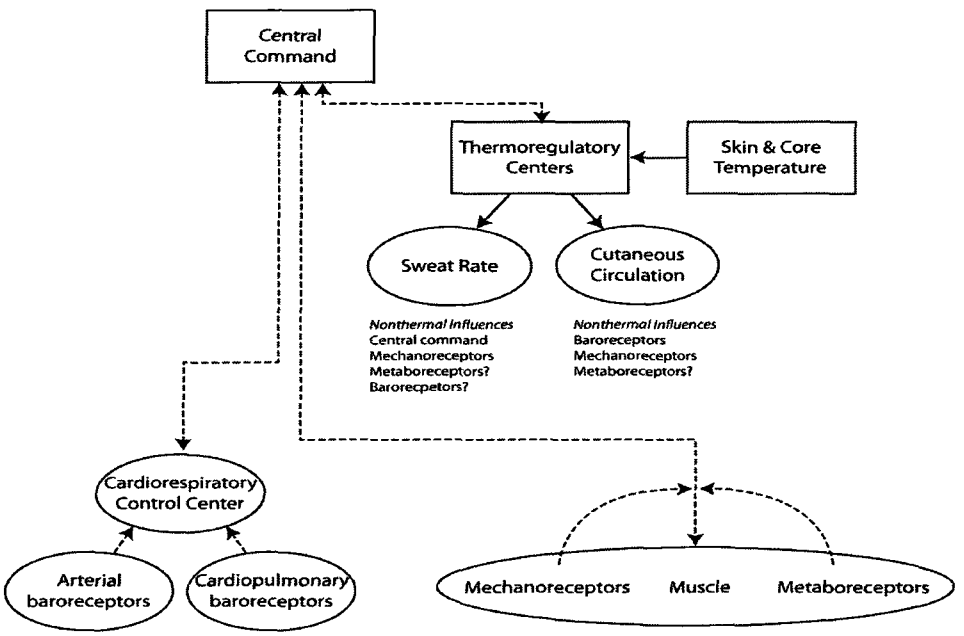

Figure 1. Schematic summary of nonthermal influences on postexercise heat loss responses. The figure presents our current understanding of these influences as concluded by the recovery mode studies discussed in the text. These studies were conducted in thermoneutral conditions using short duration moderate-intensity exercise. The '?' denoted means that the influence listed remains to be studied or is still unresolved based on the research presented in this review. Solid lines indicate known thermal influences on sweating and the cutaneous circulation. Dashed lines indicate nonthermal inputs. Source: Journeay *et al.* (2006).

Kenny *et al.* (2007) stated that "to date, the mechanisms whereby sensory information is processed and transferred to the controller, and subsequently transformed into effector signals that stimulate output, remain unclear". An understanding of the effector signals that modify vasomotor and sudomotor responses are of primary importance when discussing thermoregulation and optimal heat dissipation.

2.2 Thermoregulatory mechanisms during exercise

2.2.1 Heat Exchange

At rest, the temperature of skeletal muscle tends to be between 33°C and 35°C (Wendt *et al.*, 2007). When the body is in a resting state heat is transferred between the core (~37°C) and skeletal muscle tissue (Wendt *et al.*, 2007). During exercise, increased metabolic and muscular activity increases heat production and causes muscle temperature to rise, leading to the net transfer of heat from skeletal muscle to blood and eventually to the core (Wendt *et al.*, 2007). Energy is transferred as a result of a difference in temperature (heat). The temperature gradient between core and skin determines the potential for heat transfer to the periphery (Wendt *et al.*, 2007). Heat energy is transferred down a temperature gradient from high to low temperature. An increase in core temperature leads to an increase in skin blood flow and sweating. At an increased ambient temperature heat loss occurs primarily through evaporative heat loss (Wendt *et al.*, 2007). Sweat can only be effective for cooling if it evaporates. Evaporation is reduced when the relative humidity in the air is high due to the low water vapour pressure gradient (Wendt *et al.*, 2007). Wet air contains a high amount of water vapour, reducing the gradient and therefore the amount of sweat that evaporates. Therefore, sweat

accumulates with little loss of body heat (Wendt *et al.*, 2007) leading to further increases in core temperature as the rate of heat production is greater than the rate of heat loss.

Body core temperature in humans is determined by the relative rates of net metabolic heat production and net heat loss via the heat exchange avenues of conduction, radiation and evaporation. Following the onset of exercise the time taken to balance the differential rates of heat production and heat loss is known as the thermal inertia (Murgatroyd *et al.*, 1993) or temporal dissociation (Webb & Annis, 1966) (Fig. 2). At a given rate of heat production, a greater thermal inertia results in a larger change in body heat content and an increase in core temperature (Webb, 1998).

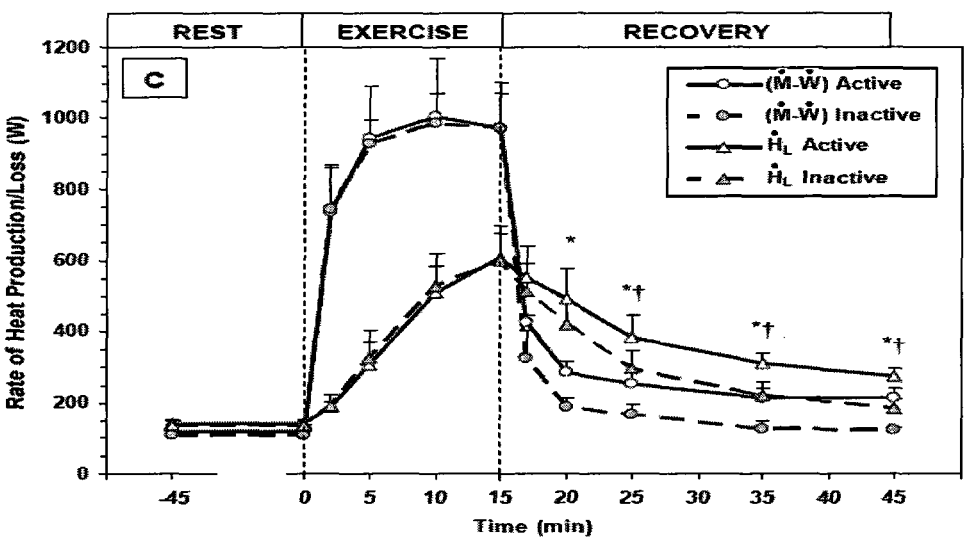

Figure 2: Mean whole-body calorimetry data for the rate of net total heat production (M˙ _ W˙) and rate of total heat loss (H˙ L) for both inactive and active postexercise recoveries. Vertical dotted lines indicate onset and cessation of exercise. Error bars indicate standard deviation. Significant difference between recovery modes are indicated by asterisk (*) for (M˙ _W˙) and dagger (†) for H˙ L. Source: Jay *et al.* (2008).

2.2.2 Exercise in the heat

The increased rate of body heat storage is exacerbated during exercise in the heat. Exercise performed in the heat leads to an elevation in core temperature due to an increase in heat production and reduced heat dissipation relative to a cool environment (Gonzalez-Alonso *et al.*, 2008). Blood flow to active muscle and the myocardium are required to meet the energetic demands for muscular activity, while blood flow to the skin is required to meet the demands of temperature regulation (Gonzalez-Alonso *et al.*, 2008). The combined demands for blood flow during exercise in the heat result in a competition for the available cardiac output, which limit the ability to meet the combined demands of exercise and of temperature regulation (Gonzalez-Alonso *et al.*, 2008). An increased heart rate becomes necessary to maintain adequate cardiac output (Nybo, 2008). Increased exercise intensities up to maximum oxygen consumption further increase the competition for adequate blood flow to working muscle and to the skin for proper heat dissipation (Gonzalez-Alonso *et al.*, 2008). At the onset of low-to moderate intensity exercise in the heat, and as long as severe hyperthermia is prevented, cardiac output may increase to meet the increased need for perfusion of the skin (Nybo, 2008). However, when the exercise intensity and the external heat load are of such magnitude that endogenous heat production surpasses the capacity for heat dissipation to the environment, hyperthermia develops and the ability to maintain cardiac output is jeopardized because stroke volume declines as core temperature increases (Nybo, 2008). The cardiac pumping capacity of a person of average physical training limits the requirements for adequate vasodilation to muscle and skin to sustain exercise in the heat (Gonzalez-Alonso *et al.*, 2008).

2.3 Thermoregulatory mechanisms postexercise

2.3.1 Thermal contributions

Thoden *et al.* (1994) were the first to report a prolonged elevation in postexercise esophageal temperature of approximately 0.4-0.5°C. This substantial increase in esophageal temperature after the completion of exercise was a major finding since heat illnesses are known to occur due to increases in core temperature that disrupt thermoregulatory mechanisms of heat dissipation. The net increase in body heat storage during exercise is induced by elevated esophageal temperature postexercise (Mekjavic & Eiken, 2006). It is well documented that following a bout of dynamic exercise a sustained elevation of core body temperature above pre-exercise resting values is evident for at least 60 to 90-min of stationary upright seated recovery (Jay *et al.*, 2008). Thoden *et al.* (1994) demonstrated that this elevation was not of metabolic origin as oxygen consumption had returned to baseline values within 5-10 min and that skin blood flow values had returned to baseline values within 10-15 min. In fact, the postexercise elevation in core temperature was shown to be equal in magnitude to the vasodilation threshold (Th_{vd}) during exercise, suggesting that thermal reflexive vasodilation was significantly reduced before pre-exercise resting core temperature could be re-established (Thoden *et al.*, 1994). Kenny *et al.* (1996) reinforced observations by Thoden *et al.* (1994) that there is a direct relationship between postexercise esophageal temperature and Th_{vd}. Increased esophageal temperature postexercise leads to an increased Th_{vd}. Therefore, a higher esophageal temperature is needed to initiate vasodilation for adequate heat dissipation during the postexercise period.

Pre-exercise core body temperature is not re-established postexercise and is contrary to what hypothalamic set-point theory of human thermoregulation would predict (Journeay *et al.*, 2006). Once heat-producing events of exercise are absent, esophageal temperature should decrease to pre-exercise levels (Journeay *et al.*, 2006). Although an increase in esophageal temperature is demonstrated postexercise, there is not an equal increase in skin blood flow and sweating to offset the rise in core temperature and to increase heat dissipation and eventually decrease core body temperature (Journeay *et al.*, 2006). In fact, skin blood flow, skin temperature, and sweating have been shown to return to pre-exercise levels even when the esophageal temperature remains elevated throughout the recovery period (Journeay *et al.*, 2006). Therefore, during postexercise recovery there is a decrease in thermal mechanisms regulating proper heat dissipation. The body maintains an elevated core temperature postexercise while mechanisms of heat dissipation are attenuated. In attempts to understand the inconsistency between an increase in core temperature and a return of heat dissipation mechanisms to baseline values, earlier investigators interpreted this discrepancy to suggest a possible resetting of the skin blood flow/sweating-esophageal temperature relationship postexercise (Journeay *et al.*, 2006). Referring to an increase in the hypothalamic "set-point" temperature at which skin blood flow and sweating are initiated. However, more recent research suggests that nonthermal factors associated with blood pressure regulation (i.e., baroreceptors) affect thermal control (Kenny *et al.*, 2007).

The rise in esophageal temperature postexercise was determined to be a consequence of exercise and not an increase in body heat content alone (Journeay *et al.*, 2006). Kenny (1996) confirmed that an increase in esophageal temperature is only

maintained during exercise recovery and not after exogenous whole-body heating in warm water (42°C). The whole-body heating was compared to 15 min of moderate intensity exercise (Kenny, 1996). Both interventions had a similar rate of rise in esophageal temperature (Kenny, 1996). The difference was that whole-body heating did not sustain esophageal temperature after the removal of the exogenous heat source (Kenny, 1996). The finding that human thermoregulatory responses postexercise have been shown to be different from that observed during exercise and contradict set-point control theory of human thermoregulation (Journeay *et al.*, 2006; Kenny *et al.*, 2007; Jay & Kenny, 2007) have stimulated further research.

2.3.2. Nonthermal contributions

Nonthermal effects on thermal control are of particular importance when investigating the decline in heat loss mechanisms during exercise recovery due to the decrease in mean arterial pressure that humans experience after the completion of exercise (Wilkins *et al.*, 2004). Leonard Hill in 1898 was the first to document a reduction in mean arterial pressure after exercise (Journeay *et al.*, 2006). The reduction in mean arterial pressure after exercise is now referred to as postexercise hypotension (Journeay *et al.*, 2006; Wilkins *et al.*, 2004). Postexercise hypotension is characterized by significant hemodynamic changes. Cardiac output is known to decrease from exercise values more rapidly then total peripheral resistance (Wilkins *et al.*, 2004). The decrease in cardiac output is due to a large portion of blood in the periphery; active and inactive muscle as well as the skin (in attempts to dissipate heat through sweating). The reduction of central blood volume in the core leads to postexercise hypotension.

Recent research has attempted to determine the nonthermoregulatory influences, baroreceptors, on thermal responses postexercise (Kenny *et al.*, 2007). However, there still remains a lack of information regarding the direct measurement of nonthermal baroreceptors effect on vasomotor and sudomotor responses postexercise (Kenny *et al.*, 2003). As noted earlier, there are two populations of baroreceptors. The arterial baroreceptors which are the higher pressure baroreceptors represented by the aortic and carotid baroreceptors. The arterial baroreflexes have been implicated as the major compensatory mechanism during changes in blood pressure (Kamijo *et al.*, 2005). The cardiopulmonary baroreceptors, which are the lower pressure baroreceptors located in the chambers of the heart and the pulmonary artery and veins, alter peripheral vascular resistance but have little effect on heart rate or cardiac output (Johnson *et al.*, 1973). When cardiopulmonary baroreceptors are activated, there are no obvious changes in blood pressure (Johnson *et al.*, 1973). Therefore, arterial baroreceptors are of particular importance when evaluating thermal responses based on changes in blood pressure.

2.3.3. Recovery posture

The position of recovery after dynamic exercise is of considerable importance due to the increase in vasodilation at active and inactive musculature. Peripheral vasodilation causes venous blood pooling in the lower extremities during exercise recovery in an upright seated position (Journeay *et al.*, 2006). Venous pooling in the lower extremities causes a decrease in the amount of blood returning to the heart and initiates baroreceptor unloading. The magnitude of decrease in mean arterial pressure is greatly influenced by the position during exercise recovery (Journeay *et al.*, 2006). A change in posture from

supine to an upright position distributes between 300 ml to 800 ml of blood to the abdomen and dependent extremities (Rowell, 1993). This peripheral pooling results in a decreased venous return and subsequent reductions in systolic blood pressure, diastolic blood pressure, stroke volume, cardiac output, and consequently mean arterial pressure. The fall in blood pressure initiates the activation of the baroreflexes, which in turn results in compensatory increases in heart rate and total peripheral resistance which tend to restore mean arterial pressure to resting levels (Berry *et al.*, 2006). Mean arterial pressure is highly regulated and its tight control is essential for the maintenance of cerebral perfusion and consciousness under the effect of gravity (Rowell, 1993). Orthostatic tolerance is defined as "a measure of the ability to prevent hypotension during gravitational stress" (Lee *et al.*, 2003). An upright seated position exacerbates venous and muscle pooling of warm blood during exercise recovery due to a higher hydrostatic pressure (Lee *et al.*, 2003). Baroreflex-mediated changes in vasomotor tone and heart rate tend to minimize the fall in arterial blood pressure (Lee *et al.*, 2003). It has been well documented that there is a larger reduction in mean arterial pressure during recovery in the upright seated position compared to the supine position (Journeay *et al.*, 2006). Recovery in the upright seated position is known to result in greater baroreceptor unloading compared to the supine position.

Several techniques have been designed to test the concept of nonthermal baroreceptor control of skin blood flow and sweating during exercise recovery. Lower body pressure applications as well as tilting maneuvers have been used to mechanically induce changes in blood pressure. Lower body positive pressure application in the upright seated position and head-down tilt have been shown to attenuate postexercise

hypotension (Jackson & Kenny, 2003; Journeay *et al.*, 2004; McInnis *et al.*, 2006). Both lower body positive pressure and head-down tilt redistribute blood towards the heart and increase central venous pressure (Cui *et al.*, 2004; Journeay *et al.*, 2004; McInnis *et al.*, 2006). The redistribution of blood towards the heart increases stroke volume and mean arterial pressure while decreasing heart rate and total peripheral resistance (Journeay *et al.*, 2004; McInnis *et al.*, 2006). Therefore, the application of lower body positive pressure and head-down tilt reverse venous blood pooling that is associated with postexercise hypotension and induces baroreceptor loading increasing local heat loss responses of skin blood flow and sweating (Jackson & Kenny, 2003; Journeay *et al.*, 2004; McInnis *et al.*, 2006). In comparison, application of negative pressure to the lower limbs and the head-up tilt position pools blood in the lower extremities and lowers central venous pressure (Cui *et al.*, 2004) subsequently unloading baroreceptors through decreases in mean arterial pressure. Therefore, negative pressure application and head-up tilt maintains venous blood pooling and baroreceptor unloading sustaining postexercise hypotension and decreasing local heat loss responses of skin blood flow and sweating (Jackson & Kenny, 2003; Cui *et al.*, 2004).

2.3.4. Recovery modes

In addition to recovery postures, different recovery modes have been developed to examine different nonthermal inputs on thermal responses during exercise recovery, which include active, inactive, and passive recovery (Gagnon *et al.*, 2008). The use of different recovery modes allows for the isolation of relative nonthermal inputs (central command, mechanoreceptors/skeletal muscle pump, and baroreceptors) on thermal

responses of skin blood flow and sweating (Gagnon *et al.*, 2008). The mechanisms of the different recovery modalities are: 1) during active recovery (loadless pedaling on a two-seated bicycle), skeletal muscle pump/mechanoreceptors and central command are activated; 2) during passive cycling, mechanoreceptors are stimulated without the involvement of central command; and 3) during inactive recovery, baroreceptors are primarily implicated (Gagnon *et al.*, 2008). An increase in venous blood pooling in the lower extremities is exacerbated by the reduction of skeletal muscle pump during inactive recovery (Gagnon *et al.*, 2008). Skeletal muscle pump is a collection of skeletal muscles that aid the heart in the circulation of blood. Skeletal muscle pump is especially important in the increase in venous return to the heart. Active and passive recovery modes effectively maintain mean arterial pressure above levels reported during inactive recovery (Gagnon *et al.*, 2008). The maintenance of mean arterial pressure in the active and passive recovery modes reduces the unloading of baroreceptors through the action of skeletal muscle pump/mechanoreceptors and/or central command effectively maintaining heat loss responses (cutaneous vasodilation and sweating) at higher levels than an inactive recovery mode (Carter *et al.*, 2002).

2.3.5 Baroreceptor effects on cutaneous vasodilation and sweating

Reductions in mean arterial pressure during inactive exercise recovery lead to the attenuation of mechanisms regulating heat dissipation (cutaneous vasodilation and sweating) (Kenny, 1996). Attenuating the degree of baroreceptor unloading by recovering in a 15° head-down tilt, maintains mean arterial pressure throughout recovery compared to the upright seated position (McInnis *et al.*, 2006). The displacement of blood from the

lower extremities to the heart during head-down tilt has been suggested to load baroreceptors, increase stroke volume, and allow for a greater amount of blood to be redistributed to the periphery to decrease core temperature through sustained elevations in cutaneous vascular conductance and sweat rate (McInnis *et al.*, 2006). In comparison, maintaining a reduction in mean arterial pressure through lower body negative pressure application leads to further displacement of blood to the lower extremities. The reduction in mean arterial pressure has been demonstrated to decrease cutaneous vascular conductance and sweat rate during exercise recovery (Journeay *et al.*, 2004). The decrease in cutaneous vascular conductance and sweat rate maintains an increased core temperature throughout exercise recovery (Journeay *et al.*, 2004). The mechanisms from previous studies suggest a nonthermal baroreceptor contribution regulating thermoregulatory mechanisms of heat dissipation. However measurements of baroreceptor sensitivity have not been quantified in previous studies to date.

2.4 Baroreceptor sensitivity (BRS)

Baroreceptors are the pressure sensors of the autonomic nervous system (Samniah *et al.*, 2004). Their function is to monitor and initiate adjustments of heart rate, vascular tone, and neuro-endocrine status in order to maintain adequate organ blood flow during various physiological and pathological conditions (Samniah *et al.*, 2004). Baroreceptor sensitivity is characterized as the amount of response in heart beat interval to a change in blood pressure, expressed in $ms \cdot mmHg^{-1}$ (Westerhof *et al.*, 2004). Cross-correlational BRS (xBRS) is classified as a time-domain method that generates values of BRS at approximately 1 value per 2 seconds. BRS is obtained from the time-domain method

from the slope of the regression line between heart interval and systolic blood pressure values. These values belong to a 10 s window of data where the heart-interval values are delayed by applying a time-shift that maximizes the cross-correlation. The technique scans the beat-to-beat series of systolic blood pressure to identify a 'sequence' (i.e., series of heart beats) in which a monotonic increase (or decrease) of systolic pressure is followed, after a delay (tau) of zero, one, or two beats, by a monotonic increase (or decrease) of heart interval. The technique assumes that the progressive changes of heart interval following the monotonic changes in systolic pressure reflect the buffering action of the baroreflex. An inverse relationship exists between changes in arterial blood pressure and changes in heart rate which suggests a negative feedback control system (Raven *et al.*, 2006). It is well known that baroreceptors play an important role in blood pressure control in the acute phase, which is immediately affected by postural changes (Ino-Oka *et al.*, 2008). However, recent studies have suggested that carotid baroreceptors may be involved in blood pressure control in the chronic phase (Ino-Oka *et al.*, 2008); though a lack of research exists in this area. Convertino and Adams, (1991) reported an increase in baroreceptor sensitivity 3- to 24-h after the completion of maximal exercise to exhaustion. Their findings suggest that intense exercise may increase the sensitivity of autonomic control of vagal withdrawal through acute, rapid adjustment of the central nervous system. The authors suggested that the use of one bout of intense exercise within 24-h of re-entry from spaceflight may represent a tenable countermeasure against the development of post-flight orthostatic hypotension.

Baroreceptor sensitivity has been demonstrated to alter with sympathovagal balance (Iida *et al.*, 1999). A reduction in BRS has been associated with a shift in

autonomic nervous system balance towards sympathetic dominance. In contrast, an increase in BRS demonstrates an autonomic nervous system shift towards parasympathetic dominance (Iida *et al.*, 1999). Normally, arterial baroreceptors tend to minimize systemic hypotension by initiating reflex vasoconstriction and tachycardia (Samniah *et al.*, 2004). However, reductions in cardiovagal BRS have been identified during exercise recovery (Niemela, 2008), obesity (Skrapari *et al.*, 2007), whole body heat stress (Lee *et al.*, 2003; Wilson *et al.*, 2002), postural stress (Westerhof *et al.*, 2006), type II diabetes (Laederach-Hofmann *et al.*, 1999), chronic cardiovascular diseases (Lanfranchi & Somers, 2002), and as a function of age (Stauss *et al.*, 1997). Reductions in BRS have been associated with impaired regulation of blood pressure, electrical instability of the myocardium, and increased risk of cardiovascular disease-related mortality (Skrapari *et al.*, 2007). Two of the parameters that influence BRS are autonomic nervous system balance and arterial distensibility (Skrapari *et al.*, 2007). BRS is attenuated wherever sympathetic nervous system activity is enhanced and when central arterial compliance is reduced (Skrapari *et al.*, 2007). Insight into baroreflex behaviour is of clinical relevance, since an attenuated baroreflex represents a negative prognostic factor in cardiovascular diseases (Skrapari *et al.*, 2007).

2.4.1 During exercise

Previous experimentation conducted on both animals and humans has demonstrated that baroreceptors continue to function to regulate arterial pressure during exercise (Joyner, 2006). However, the arterial baroreflex is reset during exercise compared to baseline resting values (Raven *et al.*, 2006; Niemela, 2008). At rest, the

heart rate response to changes in blood pressure is equal since the baroreflex response is operating at its maximal sensitivity (Ogoh *et al.*, 2005). During exercise, the baroreflex responds to a lower mean arterial pressure and a reduced gain in sensitivity (Raven *et al.*, 2006). Therefore, during exercise the baroreflex is better able to counteract hypertensive stimuli (Raven *et al.*, 2006). Input from neural mechanisms (central command, the exercise pressor reflex, and the arterial baroreflex) are essential for the normal physiological responses to exercise (Raven *et al.*, 2006).

2.4.2 Postexercise

Clinicians and researchers have suggested that the myocardium is extremely susceptible to cardiac arrhythmias and potentially fatal cardiac events during the immediate postexercise period, during which autonomic balance has not yet recovered (Parekh & Lee, 2005). Sustained reductions in the carotid arterial baroreflex in the postexercise period confirm an attenuation of the baroreflex response during exercise (Terziotti *et al.*, 2001). The shift in autonomic nervous system balance during dynamic exercise causes baroreceptor sensitivity to be depressed for approximately 25-60 minutes postexercise (Terziotti *et al.*, 2001, Niemela, 2008). The duration of time needed to restore baseline BRS is dependent on the level of exercise intensity. An inverse relationship exists between changes in BRS and exercise intensity (Niemela, 2008). Previous research has demonstrated that higher intensity exercise (80% of $\dot{V}O_2$ reserve) is associated with a greater postexercise shift in autonomic balance from parasympathetic to sympathetic dominance, with a greater delay in the restoration of pre-exercise baseline values compared with exercise at 50% of $\dot{V}O_2$ reserve (Parekh & Lee, 2005).

Baroreceptor sensitivity has been previously reported to be elevated above pre-exercise values 60-180 min after aerobic and resistance exercise (Niemela, 2008) and up to 24-h after the completion of maximal exercise to exhaustion (Convertino & Adams, 1991). However, these findings are not conclusive throughout the literature since the same measures have been reported in control subjects (no-exercise) suggesting transient fluctuations in BRS which may be independent of an exercise stress (Niemela, 2008; Eckberg & Kuusela, 2005).

2.4.3 Postural stress

The autonomic nervous system is a principal component in both the short and long-term responses to positional change. In a normal subject, ~25 to 30% of the circulating blood is in the thorax (Berry *et al.*, 2006). Upon assuming an upright posture, there is a gravity-mediated downward displacement of ~300 ml to 800 ml of blood to the abdomen and dependent extremities (Rowell, 1993). This constitutes a volume drop of 26-30% with up to 50% of this fall occurring within the first few seconds of standing. Almost 25% of the body's total blood volume may be involved in this process (Rowell, 1993). This rapid redistribution in central blood volume causes a decline in venous return to the heart. Therefore, stroke volume declines about 40% due to the decrease in cardiac filling pressure (Berry *et al.*, 2006). Assumption of an upright posture leads to a displacement of blood towards the lower body, and sets into motion a cascade of hemodynamic and autonomic adjustments (Cooke *et al.*, 1999). Right and left ventricular stroke volumes decline, heart rate increases secondary to parasympathetic vagal withdrawal and sympathetic stimulation; and muscle sympathetic nerve activity and

forearm vascular resistance increase (Cooke *et al.*, 1999). Typically, the use of a head-up tilt posture is used to simulate upright posture and to mechanically induce changes in blood pressure. Cooke *et al.* (1999) demonstrated that head-up tilt progressively decreases vagal baroreflex gain and vagal cardiac nerve activity. An increase in arterial pressure occurs during passive head-up tilt. Arterial baroreceptor denervation leads to orthostatic hypotension in animals and humans, but cardiopulmonary denervation does not (Cooke *et al.*, 1999). Therefore, the most significant factor that tends to compensate for continued orthostatic stress appears to be the arterial baroreceptor influence (in particular those of the carotid sinus) or peripheral vascular resistance (Berry *et al.*, 2006). Crandall et al. (2000) suggested that the inability of the arterial baroreceptors to perform adequately may result in a failure of the system to compensate to a sudden or prolonged postural challenge. Moreover, they note that this would lead to a state of hypotension which, if sufficiently profound, could lead to cerebral hypoperfusion and loss of consciousness.

The use of posture as a non-invasive method to measure baroreceptor sensitivity has been growing in popularity due to its practicality without the use of drug interventions that may be potentially harmful in a clinical setting. It has been determined that passive tilt maneuvers and pharmacologically determined BRS are complementary measures (Parlow *et al.*, 1995). The sensitivity of the cardiac baroreflex has been demonstrated to decrease linearly with a greater vertical body axis in the head-up tilt position (Westerhof *et al.*, 2006). Increases in hypotension elicited through head-up tilt stimulate the autonomic nervous system to respond by initiating parasympathetic withdrawal and sympathetic activation (Samniah *et al.*, 2004). However, during volume

loading of the central circulation (i.e., head-up tilt to supine position) the autonomic nervous system responds by inhibiting sympathetic activity while activating parasympathetic activity (decreased heart rate and diminished vasoconstriction). Irregularities in the baroreceptor feedback system (changes in blood pressure and heart rate) can provide significant information pertaining to the proper functioning of the autonomic nervous system in a non-heat stress condition relative to a heat stress situation.

2.4.4 During heat stress

In a hyperthermic condition the cardiovascular system increases skin blood flow to the periphery tending to increase heat dissipation, which results in a reduction in central blood volume (Yamazaki *et al.*, 2001). The increase in vasodilation during a heat stress condition reduces the ability to increase total peripheral resistance. The competition between regulation of core temperature and blood pressure induces changes, including orthostatic hypotension, in the cardiovascular regulatory system (Yamazaki *et al.*, 2001). Crandall *et al.* (2000) suggested that a possible mechanism resulting in orthostatic intolerance during heat stress is a reduction in baroreceptor sensitivity. The primary neural structures governing thermoregulation are located in the hypothalamus, and electrical stimulation of the hypothalamus is known to modify baroreceptor activity (Crandall *et al.*, 2000). Despite the growing body of evidence that supports a possible relationship between nonthermoregulatory influences, such as baroreceptor activity and core temperature regulation there remains some controversy regarding baroreflex control of heart rate during heat stress in humans (Lee *et al.*, 2003). In healthy human subjects, the arterial baroreflex response of heart rate during heat stress has been reported to be

greater (Stauss *et al.*, 1997), not different (Yamazaki & Sone, 2000; Crandall, 2000; Cui *et al.*, 2002; Yamazaki *et al.*, 2001; Yamazaki *et al.*, 1997; Yamazaki & Sone, 2001) and attenuated (Lee *et al.*, 2003; Yamazaki *et al.*, 2003; Chin & Mackinnon, 2006) compared with that during a non-heat stress condition. The inconsistencies in previous findings were attributed to factors such as age, the method of body heating, the baroreceptor population perturbed, the magnitude of imposed heat stress, and/or the techniques used to assess baroreflex function (Lee *et al.*, 2003; Crandall *et al.*, 2000).

The arterial (aortic and carotid) baroreflexes have been implicated as the major compensatory mechanism during changes in blood pressure (Kamijo *et al.*, 2005). Crandall *et al.* (2000) reported no change in the gain of carotid-cardiac baroreflex curve during passively-induced whole body heating (i.e. esophageal temperature increase of 0.7-1.5°C) but demonstrated a significantly attenuated maximal gain of the carotid-vasomotor baroreflex (Crandall *et al.*, 2003). Both carotid-cardiac and carotid-vasomotor baroreflex curves were shifted to accommodate the slight decrease in blood pressure and substantial increase in heart rate that accompanies heat stress (Crandall *et al.*, 2003). Crandall *et al.* (2003) concluded that the carotid baroreceptor modulation of heart rate is preserved under heat stress conditions, while carotid baroreflex regulation of blood pressure is impaired. In addition to carotid baroreceptors, baroreflex control of blood pressure is also regulated by aortic and cardiopulmonary baroreceptors. Thus although assessment of carotid baroreflex function during passively-induced whole body heating is informative, it does not provide information regarding the effects of heat stress on integrated baroreflex control (Crandall *et al.*, 2000).

Integrated baroreflex function can be assessed by transfer function analysis between blood pressure and heart rate spectral variability (Crandall *et al.*, 2000). The use of transfer function gain analysis determined that passively-induced heat stress significantly reduced dynamic baroreflex regulation of heart rate within the high frequency range by approximately 50% without significantly affecting the gain in the low frequency at a sublingual temperature of 37.1+/- 0.1°C (Crandall *et al.*, 2003). Passive heat stress (i.e., whole body heating) has been shown to reduce baroreceptor sensitivity and may be indicative of the effects of heat stress on overall baroreflex regulation of blood pressure in humans (Crandall *et al.*, 2003). However suggestive; Crandall *et al.* (2000) were not able to conclude whether the reduction in baroreflex responsiveness during passively-induced whole body heating in humans is sufficient to compromise one's ability to withstand orthostatic stress. It has been suggested that heat stress contributes to reductions in BRS in two ways (Lee *et al.*, 2003). Changes in autonomic balance impact resting heart rate and alter vagal-mediated BRS (Lee *et al.*, 2003). Autonomic balance shifts during heat stress to a decrease in vagal or parasympathetic activity and an increase in sympathetic activity (Lee *et al.*, 2003). The shift in autonomic balance provides evidence to support the resultant increase in heart rate during heat stress conditions (Lee *et al.*, 2003). However, the reduction in BRS may not be attributed to heat stress directly, but to the shift in autonomic balance caused by heat stress (Lee *et al.*, 2003).

2.4.5 Combined heat and postural stress

The competition between regulation of core temperature and blood pressure is exacerbated when heat stress is combined with postural stress of an upright position.

Wilson *et al.* (2002) demonstrated that when core temperature was elevated 0.9°C by passive heating, four of nine participants were unable to remain upright (60° head-up tilt) for 10 minutes. Pre-syncopal symptoms were evident in these individuals and therefore the average duration of tilt was reduced to 6 minutes (Wilson *et al.*, 2002). In contrast, under normothermic conditions all individuals completed the 10 minute head-up tilt test. Heart rate control of the arterial baroreflex response plays an important role in maintaining blood pressure within the normal range during an orthostatic challenge (Yamazaki *et al.*, 2001) and this response is intensified during heat stress (Yamazaki & Sone 2001). Yamazaki & Sone (2001) concluded that the increased variability of arterial pressure during head-up tilt is magnified by passively-induced whole body heating. Changes in arterial pressure variability during orthostasis can be partially explained by reduced sensitivity of the spontaneous baroreflex response of heart rate during thermal stress (Yamazaki & Sone 2001). Although both heating and head-up tilt (within a range of 30-90°) decrease cardiac parasympathetic activity, the effects of the two stressors on the arterial baroreflex response of heart rate are different (Yamazaki & Sone 2001). Yamazaki & Sone (2001) reported that the cardiac baroreflex response was not altered during mild hyperthermia (esophageal temperature of 38.0°C) in the supine position. However, cardiac baroreflex response decreased at 70° head-up tilt during normothermia even when the increases in heart rate during hyperthermia and posture stress were similar (Yamazaki & Sone 2001). Therefore, it is suggested that the combined effect of heat stress and postural stress reduces the sensitivity of the spontaneous baroreflex response of heart rate.

2.5 Heart Rate Variability (HRV)

2.5.1 Definition and analyses

The amount of heart rate fluctuations around the mean heart rate (heart rate variability, HRV) can be used as a reflection of the cardiorespiratory control system providing information regarding the balance between sympathetic and parasympathetic function of the ANS (Van Ravenswaaij-Arts *et al.*, 1993). Reductions in HRV have been documented during acute and chronic illness (Goldberger *et al.*, 2002) and aging (Ferrari, 2002 and Goldberger *et al.*, 2002). Although other factors are likely present in the mitigation of decreased variability, change in autonomic modulation has been regarded as a major determinant.

Frequency-domain measures of HRV can provide insight into the balance between the branches of the ANS, and thus have potential diagnostic and prognostic significance (Pober *et al.*, 2004). More specifically, power spectral analysis of HRV can provide an index of autonomic balance by separating the cyclical variations in heart rate into those occurring at high-frequencies (0.15-0.4 Hz) which appear to be the result of vagal modulation, and those occurring at lower frequencies (0.04-0.15 Hz) which are believed to reflect both sympathetic and vagal modulation. In addition, the ratio of low- to high-frequency components has been proposed as a measure of cardiac sympatho-vagal balance (Parekh & Lee, 2005).

2.5.2 Effects of exercise, heat and postural stress

Independent factors such as exercise, heat exposure and/or orthostatic challenges are known to affect HRV. Decreased HRV has been reported immediately after acute

endurance exercise demonstrated by an attenuated cardiac vagal modulation and/or a sympathetic predominance for ~30 min postexercise (Parekh & Lee, 2005, Terziotti *et al.*, 2001). The decreased variability after exercise demonstrates ANS alterations attributed to a sustained overactivity of the efferent sympathetic nervous system. Furthermore, passive heat exposure resulting in an increase in core temperature (i.e., sublingual temperature increase of 0.5°C) has been demonstrated to induce an activation of the sympathetic nervous system and a withdrawal of the parasympathetic nervous system after 30 min (Yamamoto et al., 2007). Changes in HRV are known to occur during postural stress such that with greater levels of HUT, HRV is reduced (Butler *et al.*, 1994). Specifically, a decrease in high-frequency power has been previously reported during postural transition from supine resting to 70° HUT (Iellamo *et al.*, 2001).

In addition to alterations in HRV during the short-term recovery period after exercise, previous investigators have reported attenuations in HRV (a decreased vagal modulation of the heart) for up to 24-h after exhaustive exercise (Bernardi *et al.*, 1997, Furlan *et al.*, 1993, Hautala *et al.*, 2001). These findings suggest that exhaustive exercise may decrease the contribution of the parasympathetic nervous system control of resting cardiac function for as long as 24-h following the cessation of exercise.

2.6 Hyperthermia

Hyperthermia is caused by a misalignment of thermogenic and thermolytic mechanisms. The ANS functions in maintaining a constant internal environment (Yamamoto *et al.*, 2007). The preoptic-hypothalamic unit is one of several areas of the brain involved in control of autonomic function (Benarroch & Chang, 1993). Moreover,

the preoptic region of the hypothalamus contains the central components governing thermoregulation. Therefore, changes in core temperature sensed by the hypothalamus may affect autonomic function.

Thermal strain is typically accompanied by high levels of cardiovascular strain characterized by an impairment of blood pressure and/or reductions in blood flow to the brain and splanchnic tissues (Cheung, 2007). During exercise, cerebral temperature is known to rise in parallel with core temperature (Nybo, 2008). The development of central nervous system fatigue and subsequent physical exhaustion coincides with the attainment of a critical core temperature (~40°C) during exercise. Elevated central brain temperature has been shown to have a modulating effect on motor activity (Cheung, 2007; Nybo, 2008). While studies eliciting hyperthermia via exercise in the heat have generally supported a dominant central impairment of neuromuscular activation, the impact on visceral motor (involuntary) activity of the ANS remains unclear.

2.6.1 Recovery from exercise-induced hyperthermia

Gagnon et al. (2008) showed that exercise-induced hyperthermia (esophageal temperature 39.5°C) resulted in significant disturbances in postexercise thermoeffector activity. Through the use of recovery modes, it was determined that the relative contribution of thermal and nonthermal input on thermoeffector activity changed with the level of hyperthermia. They showed that mean arterial pressure was significantly reduced from baseline values in the inactive recovery mode compared to the active and passive modes (Gagnon *et al.*, 2008). The attenuation in mean arterial blood pressure was used as an indicator of baroreceptor drive (i.e., nonthermal input). Gagnon *et al.* (2008) showed

that in the presence of a greater thermal drive the relative contribution of thermal factors to the regulation of local sweat rate predominates over nonthermal factors in the first 50 minutes postexercise (core temperature range of 38.6°C to 37.5°C). Furthermore, thermal factors were shown to override nonthermal control of cutaneous vascular conductance during the early stages, first 10 min, of recovery (esophageal temperature increase >1.0°C). Following which, nonthermal factors override thermal factors controlling cutaneous vascular conductance (Gagnon et al., 2008). However, the major limitation of the previous study is that BRS was not directly measured. Hence, it remains unclear if exercise-induced hyperthermia alters normal baroreceptor function, and if an alteration does occur, how this influences thermoeffector activity.

PART TWO:

METHODS AND RESULTS OF THE THESIS

ARTICLE I:

Acute cardiovascular response to orthostatic stress under severe hyperthermia

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ABSTRACT

We evaluated the effects of exercise-induced hyperthermia on cardiovascular and thermoregulatory control during exposure to repeated orthostatic challenges. Eight male subjects performed orthostatic challenges in a non-exercise/non-heat stress (NH) or exercise-induced hyperthermia (EIH) state. Subjects remained supine for 30 min in a thermoneutral environment (22°C) and were subsequently exposed to three successive 6-min 70° head-up tilts (HUT1, HUT2 and HUT3), each separated by 10-min supine resting. During EIH, subjects were rendered hyperthermic (rectal temperature ≥39.5°C) by exercise in the heat (42°C) and were then transferred to a thermoneutral environment. Mean arterial pressure (MAP), total peripheral resistance (TPR), baroreceptor sensitivity (BRS), cutaneous vascular conductance (CVC) and local sweat rate (LSR) responses were evaluated at baseline, the last minute prior to HUT1 and at 2-min intervals thereafter. Values were expressed as the change from baseline prior to HUT1. ΔMAP was greater in HUT3 during EIH (17.5 ± 2.7 mmHg) versus NH (7.4 ± 3.6 mmHg) ($p < 0.05$). ΔMAP during HUT3 was paralleled by a greater ΔTPR during EIH (5.6 ± 0.8 $mmHg \cdot l^{-1} \cdot min^{-1}$) compared to NH (2.7 ± 1.4 $mmHg \cdot l^{-1} \cdot min^{-1}$) ($p < 0.05$). BRS remained depressed throughout each HUT cycle (9.0 ± 1.4 and 3.4 ± 0.5 ms/mmHg in HUT3 for NH and EIH respectively) ($p < 0.05$). Furthermore, we observed a transient reduction in ΔCVC_{max} with each HUT ($p < 0.05$) whereas no differences were observed in ΔLSR. We conclude that in the presence of postexercise hyperthermia MAP is maintained during orthostatic stress likely due to increases in TPR despite exercise-induced reductions in BRS. Further, while nonthermal baroreceptor control predominates over thermal control of CVC during the orthostatic challenge following EIH, no effect was observed in LSR.

Key words: exercise recovery, postexercise, hemodynamics, sweating, skin blood flow, orthostatic intolerance

INTRODUCTION

Exercise in the heat is associated with significant cardiovascular and thermoregulatory disturbances that can persist for a prolonged period postexercise (17, 26, 28). Following the cessation of exercise, there are profound changes in the mechanisms that regulate and determine mean arterial pressure, which result in hypotension that is both vascular and neural in origin (11). This postexercise hypotension is paralleled by thermoregulatory changes such as a delayed onset threshold for the initiation of skin vasodilation (29) and sweating (30) and a concomitant increase in the magnitude of the post-exercise elevation in esophageal and muscle temperatures (27). The magnitude of the response is influenced by the level of exercise intensity (27) and level of hyperthermia (9).

There is increasing empirical evidence indicating that nonthermal baroreceptor afferent stimuli associated with postexercise hypotension may be responsible for the efferent modulation of autonomic thermoeffector activity (18-20, 27, 34). This hypothesis has evolved from the earlier observation that a greater level of postexercise hypotension, induced by exercise of increasing intensity, results in a delay in the local onset of sweating (30) and skin vasodilation (29). This is accompanied by a concomitant increase in core and muscle temperature recovery time (19, 20, 25, 27). This is further supported by studies reporting that by attenuating the baroreceptor unloading effect of exercise recovery in the early stages of recovery via the application of positive pressure to the lower limbs (+45mmHg) (14, 19), head-down tilt (34), supine recovery (23), or active/passive cycling (9) reverses the postexercise attenuation of skin blood flow and sweat rate and elicits a shorter core and muscle temperature recovery time. Taken

together, these findings demonstrate an important physiological link between the observed postexercise cardiovascular changes and the altered thermoregulatory control.

The capacity of nonthermal baroreceptor reflexes to override thermoregulatory input during hyperthermia is critical to maintain blood pressure. However, this can significantly compromise heat loss. This is a reasonable linkage given that there is some hypothalamic control over baroreflex function (10). In humans, it is well documented that orthostatic tolerance is reduced during passive heat stress compared with normothermic conditions (15, 32, 44). When the cardiovascular reflexes are overwhelmed by the demand for circulation to the skin and other organs, such as during prolonged exposure to hot ambient conditions and/or exercise in the heat, syncope may ensue. This effect is exacerbated by a hypohydration-mediated cardiovascular strain associated with a progressive sweating-induced reduction in plasma volume (36-38, 42). However, the effect of orthostasis during postexercise hyperthermia on cardiovascular and thermoregulatory control remains unclear. This has important consequences for those encountering orthostatic challenges after activity-induced hyperthermia such as pilots, astronauts and athletes.

The following study was conducted to evaluate the postexercise cardiovascular and thermoregulatory responses to postural stress performed following exercise-induced hyperthermia (end of exercise rectal temperature $\geq 39.5^{\circ}C$). Specifically, we employed an exercise paradigm which has previously been shown to elicit a pronounced reduction in arterial blood pressure paralleled by attenuated heat loss responses (8, 18-20, 27, 34). We evaluated the hypothesis that acute cardiovascular responses to repeated orthostatic stress will be attenuated following exercise-induced hyperthermia. Further, we also evaluated

the hypothesis that despite a greater level of hyperthermia, there will be a reduction in CVC and LSR during the orthostatic challenge.

METHODS

Participants

Following approval of the experimental protocol from the University of Ottawa Research Ethics Committee, 8 healthy (no history of respiratory, metabolic or cardiovascular disease) and physically active males participated in the study. Body adiposity and maximum oxygen consumption ($\dot{V}O_{2peak}$) were measured a minimum 48 h before the experimental trials. The hydrostatic weighing technique was used to determine body density and calculation of the percentage of body fat was used based on the Siri equation (45). Maximum oxygen consumption was measured during a progressive treadmill running protocol and the data were used to select the submaximal workload (~65%) for the experimental exercise phase of the study. Participants characteristics were as follows; aged (22 ± 3 yrs), height (177 ± 4 cm), weight (73 ± 6 kg), body surface area (1.89 ± 0.09 m^2), body fat (14.6 ± 5 %), $\dot{V}O_{2peak}$ (62.8 ± 7.2 $ml \cdot kg^{-1} \cdot min^{-1}$) and (4561 ± 422.1 $ml \cdot min^{-1}$).

Experimental protocol

Subjects were instructed to avoid physical activity and excessive stressors such as exposure to hot or cold temperatures, particularly during the period between awakening and experimentation and during transit from home to the laboratory. Trials were performed at the same time of day for each subject to avoid circadian variation in core

and skin temperatures. Subjects were asked to fast at least 2 h prior to experimentation, and water ingestion was permitted *ad libitum* during this time to promote euhydration. However, water consumption was restricted at the start of each experimental trial. On arrival at the laboratory for each experimental trial, subjects clothed in shorts and athletic shoes were fitted with the appropriate instruments.

Each subject performed two experimental trials. During the first experimental session in a non-exercise/non-heat stress state (NH), subjects remained resting in the supine posture for 30 min in a thermoneutral ambient condition with ambient temperature of 22°C. At the end of the baseline period, subjects were exposed to three consecutive 6-min 70° head-up tilts (HUT1, HUT2 and HUT3), separated by a 10-min supine recovery (SUP1, SUP2 and SUP3). During the second (exercise-induced hyperthermia, EIH) experimental trial subjects remained resting in the supine for posture for 30-min. At the end of the baseline resting period, subjects entered an adjoining temperature-controlled chamber maintained at 42°C where they performed treadmill running at about 65% of their predetermined $\dot{V}O_{2peak}$ until rectal temperature reached 39.5°C (24 ± 5 min). Immediately following the cessation of exercise, the participants were transferred back to a thermoneutral ambient condition (22°C) where they remained seated in an upright posture for ~15 min. They were then placed on a tilt-table in a supine posture for 15-min and subsequently exposed to three consecutive 6-min 70° HUT, separated by 10 min recovery in the supine posture.

Measurements

Rectal temperature (T_{re}) was monitored continuously using a pediatric thermocouple probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical, St-Louis, MO, USA) inserted 12 cm past the anal sphincter. Esophageal temperature (T_{es}) was measured by placing a pediatric thermocouple probe of approximately 2 mm in diameter (Mon-a-therm Nasopharyngeal Temperature Probe, Mallinckrodt Medical, St-Louis, MO, USA) through the participant's nostril while they were asked to sip water through a straw. The location of the probe tip in the esophagus was estimated to be at the level of the eighth and ninth thoracic vertebrae (35).

Skin blood flow (SkBF) was estimated using laser-Doppler velocimetry (Periflux System 5000, main control unit; PF5010 LDPM, operating unit; Perimed AB, Stolkholm, Sweden) at the right midanterior forearm such that the arm was level with the heart. Prior to the start of the experimental trial, the laser-Doppler flow probe (PR 401 Angled probe, Perimed AB, Stockholm, Sweden) was taped to cleaned skin in an area that, superficially, did not appear to be highly vascular and from where consistent readings were noted. Once secured to the skin surface, the probe was not removed from its location. At the end of each experimental trial, a heating element (PF 5020 temperature unit, Perimed) which houses the laster-Doppler flow probe, was activated to elevate local skin temperature to 42°C until maximum skin blood flow was measured (~30-45 min). Cutaneous vascular conductance (CVC) was calculated as the ratio of laser-Doppler flow to MAP and data are presented as a percentage of maximum CVC (%CVC_{max}).

Local sweat rate (LSR) was estimated from a 5.0-cm^2 ventilated capsule placed on the trapezius. Anhydrous compressed air was passed through the capsule over the skin

surface at a rate of 0.7 L/min. Water content of the effluent air was measured at a known barometric pressure, using the readings from an Omega HX93 humidity and temperature sensor (Omega Engineering, Stamford, CT). Local sweat rate was calculated using the difference in water content between effluent and influent air, and the flow rate. This value was normalized for the skin surface area under the capsule and was expressed in milligrams per minute per square centimeter.

Heart rate (HR) was monitored using a Polar coded transmitter, recorded continuously and stored with a Polar Advantage interface and Polar Precision Performance software (Polar Electro Oy, Finland). Mean arterial pressure (MAP), cardiac output ($\dot{Q}$), and baroreceptor sensitivity (BRS) were estimated from the integration of a non-invasive recording of blood pressure at the middle digit of the right hand (Finapres 2300, Ohmeda, Madison, WI, USA) fixed at heart level (the third intercostal space). MAP was also verified periodically throughout the protocol by auscultation of the brachial artery. Stroke volume (SV) was calculated as $\dot{Q}$/HR. Total peripheral resistance (TPR) was calculated as MAP/$\dot{Q}$. For BRS, the Beatfast software (BeatScope 1.1a, Amsterdam, The Netherlands) was used to determine beat-to-beat variables, interbeat interval (IBI) and systolic, diastolic, and mean arterial pressures. Systolic blood pressure and IBI were used to calculate BRS in ms/mmHg (47).

A Teeter Hang Ups F5000 inversion table was used to manipulate posture. The angle of the tilt was measured using a Unitek Magnetic Polycast Protracter.

Statistical Analyses

A one-way repeated measures analysis of variance (ANOVA) was used to analyze the baseline absolute values for each variable between days. For each cycle of HUT and supine recovery, a two-way repeated measures ANOVA was used to analyze the absolute and relative changes from baseline in HR, SV, MAP, $\dot{Q}$, TPR, T_{re}, CVC and LSR using the repeatable factors of experimental session (levels: Day 1, no-exercise/no-heat stress; and Day 2, exercise-induced hyperthermia), and time (levels: 2, 4 and 6 min for HUT1, HUT2 and HUT3 respectively; and 2, 4, 6 and 10 min for SUP1, SUP2 and SUP3 respectively). For the purpose of this presentation, with the exception of the BRS data, only relative changes (Δ) are presented in the results. Absolute values can be found in table 1. For CVC and LSR we also examined the change in response during the transition between postures. Values were compared between the last-minute of SUP and the second minute of the subsequent HUT for each of the successive SUP/HUT cycles (i.e., Baseline-HUT1, SUP1-HUT2 and SUP2-HUT3 respectively). We compared the change from baseline in BRS between NH and EIH conditions (levels: Day 1 and Day 2), and between postural position (levels: HUT and SUP). BRS values were averaged over the last 2 min of each postural position. The last min in the supine position after exercise just prior to HUT1 was used as the baseline value on Day 2 for each dependent variable. Pair-wise comparisons were performed using paired sample t-tests. The level of significance was set at 0.05 and the alpha level was adjusted during multiple comparisons so as to maintain the rate of type I error at 5% during Holm-Bonferroni post-hoc analysis. All analyses were performed using the statistical software package SPSS 17.0 for Windows (SPSS Inc. Chicago, IL, USA).

RESULTS

There were no significant differences between treatment days for absolute baseline values of MAP (p=0.163), HR (p=0.208), TPR (p=0.412), SV (p=0.460), BRS (p=0.587), $\dot{Q}$ (p=0.711), CVC (p=0.627), SR (p=0.110) and T_{re} (p=0.541) during baseline supine resting (Table 1).

Hemodynamic Responses

ΔMAP The relative change in MAP over time was constant during each of the HUT exposures HUT1 (p=0.546), HUT2 (p=0.609) and HUT3 (p=0.128). There was no effect of treatment day in the pattern of response for the ΔMAP during HUT1 (p=0.394) and HUT2 (p=0.145). However, ΔMAP in HUT3 differed between days ($p \leq 0.05$) (Fig. 2). No subjects became pre-syncopal during the trial.

There was a main effect of time on ΔMAP during SUP2 and SUP3 ($p \leq 0.05$) but not SUP1 (p=0.057). Responses were significantly different between NH and EIH for SUP2 and SUP3 only ($p \leq 0.05$) (Figure 2).

ΔTPR The relative change in TPR (ΔTPR) over time was constant during HUT2 (p=0.184) and HUT3 (p=0.289). However, values were significantly reduced over time for HUT1 ($p \leq 0.05$). ΔTPR was not significantly different between days in HUT1 (p=0.184) and HUT2 (p=0.129) but differed between days in HUT3 ($p \leq 0.05$) (Fig. 2).

There was a main effect of time on the ΔTPR during all SUP cycles ($p \leq 0.05$). No differences were observed between treatment days during any SUP period (Fig. 2).

ΔHR The relative change in HR (ΔHR) over time was similar during HUT1 (p=0.096) and HUT3 (p=0.065) but not HUT2 ($p \leq 0.05$). ΔHR was not significantly different between days for any HUT period (Fig. 1).

There was a main effect of time on ΔHR during all SUP cycles ($p \leq 0.05$). ΔHR was significantly different between days for SUP1, SUP2 and SUP3 respectively ($p \leq 0.05$) (Fig. 1).

$\Delta\dot{Q}$ There was a main effect of time on $\Delta\dot{Q}$ during all HUT periods ($p \leq 0.05$). Responses differed between treatment days for HUT3 ($p \leq 0.05$) only (Fig. 2).

There was a decrease in $\Delta\dot{Q}$ over time for all SUP periods ($p \leq 0.05$). However, no differences were observed between treatment days (Fig. 2).

ΔSV There was a main effect of time on ΔSV during HUT1 and HUT2 only ($p \leq 0.05$). There was a main effect of treatment day on the ΔSV in HUT2 and HUT3 only ($p \leq 0.05$) (Fig. 1).

There was a main effect of time on ΔSV for all SUP periods ($p \leq 0.05$) and responses were significantly different between treatment days ($p \leq 0.05$) (Fig. 1).

ΔBRS Absolute values of BRS were significantly reduced throughout each HUT and SUP maneuver between days ($p \leq 0.05$) (Table 2). Further, BRS values were significantly different from the preceding SUP to HUT for both NH and EIH ($p \leq 0.05$) (Table 2).

ΔBRS was significantly different between days ($p \leq 0.05$); such that the ΔBRS was significantly greater during NH compared to EIH in HUT1, HUT2 and HUT3 (Fig. 3).

In the supine position, ΔBRS differed significantly between days such that NH was significantly lower than EIH in SUP2. There was no significant differences between days reported in SUP1 ($p=0.120$) and SUP3 ($p=0.041$) (Fig. 3).

Thermal responses

ΔCVC There was no main effect of time on ΔCVC during HUT. However, ΔCVC was significantly different between treatment days in HUT1, HUT2 and HUT3 respectively ($p \leq 0.05$) (Fig. 4).

In the supine position, no change in ΔCVC was observed for SUP2 ($p=0.154$) and SUP3 ($p=0.847$). A decrease over time for SUP1 was measured ($p \leq 0.05$). The ΔCVC was significantly different between treatment days in SUP1, SUP2 and SUP3 ($p \leq 0.001$) (Fig. 4).

In comparing the change in response during the transition from SUP to HUT, we observed a significant difference in ΔCVC during each SUP/HUT cycles ($p \leq 0.05$) (Fig. 4).

ΔLSR There was no main effect of time on ΔLSR during any HUT period (Fig. 4). However, ΔSR was significantly different between days in HUT1, HUT2 and HUT3 respectively ($p \leq 0.05$) (Fig. 4).

Differences in SUP were similar to those of HUT. The ΔLSR did not differ over time, however significant differences were found between treatment days in each SUP cycle (Fig. 4).

No observed differences in ΔLSR during the transition between SUP and HUT for any of the three SUP/HUT cycles.

T_{re} There was not a main effect of time on ΔT_{re} during HUT. However, a difference in the response profile was observed between treatment days for HUT2 and HUT3 ($p \leq 0.05$) (Fig. 4).

In the supine position, we observed a main effect of time in ΔT_{re} for all SUP cycles ($p \leq 0.05$). In addition, ΔT_{re} was different between treatment days for SUP2 and SUP3 only ($p \leq 0.05$) (Fig. 4).

DISCUSSION

We show that despite a reduced stroke volume following exercise-induced hyperthermia (EIH), the cardiovascular system maintained MAP and $\dot{Q}$ during repeated 70° head-up tilts. This was true despite the known exercise-induced changes in the recovery hemodynamics and thermal responses as evidenced in this study by the observed reduction in MAP and elevated rectal temperature prior to and during the repeated orthostatic challenge (Table 1). We show that under conditions of significant postexercise hypotension and decreased baroreceptor responsiveness, that the relative increase in TPR and SV became more pronounced with successive tilts. This response led to a progressive reestablishment of MAP to baseline resting levels. This suggests that

the observed improvement in MAP with repetitive orthostatic challenges in a hyperthermic state appears to be driven largely by an increase in TPR that remains responsive despite an exercise-induced reduction in baroreflex sensitivity. Furthermore, we observed a rapid attenuation of CVC in the HUT position despite a significant thermal drive as evidenced by a sustained postexercise elevation of rectal temperature. This provides further evidence in support of a postexercise nonthermal baroreceptor mediated influence on skin perfusion. In contrast, we show that the temporal pattern of thermoregulatory sweating remained largely unaffected by repeated orthostatic challenges suggestive of an overriding thermal influence.

Hemodynamic responses to repeated postural stress

Under normothermic conditions, passive tilting from supine to an upright posture results in a redistribution of blood from the central core region to the legs (~500 mL) and between 200-300 mL is pooled in the pelvic region (1). The resultant pooling of blood in the lower extremities causes a decreased venous return leading to reductions in systolic and diastolic blood pressure, SV, $\dot{Q}$, and consequently MAP. This fall in blood pressure initiates the activation of arterial and cardiopulmonary baroreflexes to help restore MAP to resting levels (1). The capacity of nonthermal baroreceptor reflexes to override thermoregulatory input, such as during hyperthermia, is critical to maintaining blood pressure. In thermoneutral environments, skin receives ~500 mL or 5-10 % of cardiac output (5, 40, 41). However, in conditions of heat stress, up to 8 liters per minute or 50-70 % of cardiac output can be shifted to the skin (5, 40, 41). Under a hyperthermic state,

the redistribution of blood from the skin is essential in maintaining adequate blood pressure control during an additional orthostatic challenge.

When humans are heated to mild to moderate levels of hyperthermia (core temperature ≤1.5°C above baseline resting) (3) the vasoconstrictor function is maintained when an orthostatic stress is introduced (4, 6, 7, 15, 21). It is thought that the baroreflex exerts its action via the withdrawal of active vasodilator activity (22), however more recent work has also implicated altered vasoconstrictor responsiveness under whole-body heating conditions (3, 49). Whether this capacity exists at severe levels of hyperthermia (core temperature >1.5°C above baseline resting) remained to date unresolved. In the present study, during a sustained postexercise hyperthermia, we show that the relative changes in MAP during postural stress of 70° HUT were more pronounced with successive tilts as blood pressure gradually returned to near baseline levels. We show that during HUT1 an average increase in MAP of 9 ± 2 mmHg was measured compared to an increase of 16 ± 3 mmHg in the final HUT3 following EIH. The progressive reestablishment of blood pressure appears to be driven largely by an improvement in TPR in part as the result of a redistribution of blood away from skin as evidenced by a progressive decrease in skin perfusion. This is further supported by the time-dependent changes in $\dot{Q}$ and SV. Of note, we show that the increase in TPR occurred despite a sustained reduction in BRS throughout exercise recovery. This suggests that vascular responsiveness and consequently arterial blood pressure control during an orthostatic challenge remains largely unaffected despite an exercise induced reduction in baroreflex sensitivity.

Baroreceptor sensitivity

Recent reports have demonstrated that baroreceptor sensitivity (a measure of reflex cardiac vagal responsiveness) (33) is depressed during the exercise recovery period (39) and during a HUT gravitational stress (47, 13) under conditions of normothermia. Niemela *et al.*, (39) reported reductions in baroreceptor sensitivity for a period of 60 min after exercise in normothermic conditions. Furthermore, it has been suggested that baroreflex control of sympathetic outflow may be altered by prior exercise (12) contributing to the reduced TPR after exercise. In the present study, we showed a significant reduction in baroreceptor sensitivity throughout the postexercise recovery period. In the early stages of recovery and prior to the start of the repetitive tilts BRS was 4.2 ± 0.4 ms/mmHg as compared to 20.6 ± 4.7 ms/mmHg for the non-exercise/non-heat stress control condition. In fact, BRS remained significantly reduced even at the end of the 78 min postexercise treatment period (22.3 ± 3.5 ms/mmHg in SUP3 during NS compared to 16.8 ± 3.7 ms/mmHg following EIH) even though MAP was re-established to baseline resting levels. While it is evident that a longer recovery period is required to restore BRS to baseline resting values, it is unclear if the depression in BRS is influenced by the level of hyperthermia (rectal temperature remained elevated by ~0.4°C at the end of the trial), the postural stress or a combination of both.

Postural or gravitational stress has been shown to modulate BRS under normothermic conditions. Westerhof *et al.*, (47) showed that the sensitivity of the cardiac baroreflex in the time domain decreases with increasing tilt angle (i.e., from -20° to +90°). The decrease in BRS was demonstrated by a shift toward longer delays between systolic blood pressure and interbeat interval and supports the suggestion that the

decrease is a result of the vagal withdrawal associated with larger postural stress (47). In the present study, we observed significant reductions in BRS under non-heat stress conditions during postural stress from the supine to the 70° head-up tilt posture (baseline supine 20.6 ± 4.7 compared to HUT1 8.1 ± 1.6). Further, despite the observed reduction in BRS following EIH, baroreflex responsiveness was still evident during postural stress albeit the magnitude of the response was reduced as compared to the non-exercise/non-heat stress (NH) condition (Fig. 3). The reduction in the range of responsiveness of the baroreflex supports previous suggestions that heat-stress induced reductions in orthostatic tolerance may be an indication that heat stress reduces the range in which baroreflexes can increase sympathetic activity during a hypotensive challenge (3). The extent to which this response can be maintained in the face of a postural stress performed in a hyperthermic state is unclear. Although we did not observe signs of heat-induced and/or postural induced syncope in any of our participants during the 6-min HUT period, it is possible that the orthostatic tolerance could be compromised with longer duration tilts especially when performed in the early stages of exercise recovery.

Thermal and nonthermal factors

Studies show that local skin blood flow and sweating responses are attenuated following exercise despite sustained elevations in core and muscle temperature (2, 16, 17, 19, 24, 25, 27, 34, 46, 48). This effect is greater during recovery from exercise of increasing intensity (27, 28). This perturbation in postexercise thermoregulatory control has been ascribed to nonthermal baroreceptor input associated with a postexercise hypotension response (16, 24-26, 31, 48). These findings demonstrate that factors

determining postexercise cardiovascular status have a strong influence on thermoregulatory responses during heat stress. We show that with elevations in core temperature significant reductions in skin perfusion were observed in each HUT period. The response was most pronounced at higher levels of hyperthermia (Fig. 4). Specifically, we observed a 12% reduction in CVC during the transition from postexercise supine resting to HUT1 as compared to only a 5% reduction during the last postural transition (SUP2 to HUT3 transition). This was paralleled by a greater reduction in MAP in the early stages of exercise recovery. Our findings are consistent with previous reports of a baroreceptor modulation of CVC during postexercise hypotension, such that thermal factors override nonthermal baroreceptor mediated control of CVC when core temperature is greater than >1.0°C above baseline resting (9). Subsequent reductions in core temperature resulted in nonthermal control predominating over thermal factors in the control of CVC. Thus, despite a significant elevation in core temperature at the start of HUT (~0.7°C), it appears that CVC was strongly influenced by nonthermal baroreceptor input.

Similar to skin blood flow control, studies show that application of LBPP or 15° HDT attenuates the postexercise reduction in LSR and decreases core temperature recovery time at mild to moderate levels of hyperthermia (14, 19, 34). This is thought to be due to baroreceptor activity. While the data regarding baroreceptor influence on the cutaneous circulation is consistent, sweat rate findings are less conclusive. Gagnon *et al.*, (9) showed that in the presence of a greater thermal drive the relative contribution of thermal factors to the regulation of LSR predominates over nonthermal factors in the first 50 minutes postexercise (core temperature range of 38.6°C to 37.5°C). Consistent with

these findings we did not observe transient changes in sweating response during HUT that would support a nonthermal baroreceptor mediated influence. Rather, LSR decreased progressively over the course of the 3 successive SUP/HUT cycles (Fig. 3). However, further studies are required to evaluate this response under conditions of enhanced sweating such as during the administration of neostigmine (an acetylcholinesterase inhibitor) which is used to augment sweating (43) in order to verify these findings.

Summary

We conclude that despite substantial postexercise hypotension, elevations in core temperature and reductions in baroreceptor sensitivity elicited through exercise performed in the heat, the cardiovascular system maintained MAP and $\dot{Q}$ during repeated 70° head-up tilts. Regardless of a strong thermal drive, sustained reductions in CVC were observed with each HUT which may be indicative of a nonthermal baroreceptor mediated modulation of CVC. Indeed, the reduction in CVC was greatest during the early stages of recovery when reductions in arterial pressure were most pronounced. In contrast, a nonthermal baroreceptor mediated attenuation of LSR was not observed which may indicate that LSR is unaffected by baroreflex mediated influences under a state of elevated hyperthermia.

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Table 1. Hemodynamic and thermoregulatory responses during a repeated orthostatic challenge under a non-exercise/non-heat stress state and following exercise-induced hyperthermia.

					HUT1			SUP1		HUT2		SUP2		HUT3		SUP3	
Measure	**Day**	**Preexercise**	**End of Exercise**	**Last min Supine**	**2-min**	**6-min**	**8-min**	**16-min**	**18-min**	**22-min**	**24-min**	**32-min**	**34-min**	**38-min**	**40-min**	**48-min**
HR (beats•min^{-1})	NH	58 (3)			76 (4)	76 (3)	57 (3)	58 (3)	72 (3)	75 (4)	61 (5)	58 (3)	72 (3)	75 (4)	60 (5)	55 (3)
	EIH	61 (3)		98 (3)	125 (6)*	126 (6)*	96 (4)*	86 (4) *	113 (6) *	116 (6) *	88 (3) *	82 (4) *	106 (5) *	111 (6) *	82 (3) *	73 (6) *
MAP (mmHg)	NH	90 (3)			98 (2)	95 (4)	92 (2)	94 (2)	97 (3)	97 (3)	92 (3)	92 (3)	98 (3)	97 (4)	94 (3)	92 (3)
	EIH	86 (2)		81 (5)	87 (5)	91 (3)	92 (5)	87 (4)	92 (4)	92 (3)	92 (3)	86 (4)	96 (4)	98 (5)	94 (5)	88 (4)
TPR (mmHg•l^{-1}•min)	NH	15.2 (0.8)			17.9 (1.0)	16.3 (1.4)	15.4 (0.7)	15.9 (0.6)	18.4 (0.9)	17.2 (1.4)	15.4 (0.8)	16.1 (0.8)	18.2 (0.9)	17.7 (1.5)	16.1 (1.0)	16.8 (0.9)
	EIH	14.6 (1.0)		12.2 (0.5)	15.5 (1.0)	15.5 (1.0)	12.1 (0.8) *	13.6 (0.8) *	17.0 (0.5)	16.8 (1.0)	13.2 (0.9)	14.1 (1.0)	18.1 (0.9)	17.7 (1.0)	12.8 (0.8)	14.6 (1.5)
CVC (%max)	NH	16 (4)			14 (3)	15 (3)	18 (5)	16 (5)	13 (2)	14 (3)	18 (6)	18 (5)	14 (3)	15 (4)	17 (5)	17 (5)
	EIH	17 (3)		50 (6)	36 (4) *	30 (4) *	37 (6)	29 (6)	21 (3) *	21 (3)	28 (6)	24 (4)	18 (2)	19 (3)	25 (5)	24 (4)
SR (mg • min^{-1} • cm^{-2})	NH	0.001 (0.00)			0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)	0.001 (0.00)
	EIH	0.001 (0.00)		1.192 (0.3)	1.059 (0.3) *	1.015 (0.3) *	0.968 (0.3) *	0.777 (0.2) *	0.708 (0.2) *	0.683 (0.2) *	0.678 (0.3)	0.574 (0.2)	0.557 (0.2)	0.527 (0.2)	0.522 (0.2)	0.467 (0.2)
Tre (°C)	NH	37.01 (0.14)			36.96 (0.12)	36.98 (0.12)	36.96 (0.12)	36.91 (0.12)	36.93 (0.12)	36.98 (0.13)	36.97 (0.12)	36.96 (0.11)	36.96 (0.12)	36.99 (0.13)	37.01 (0.12)	36.94 (0.10)
	EIH	36.97 (0.07)	39.78 (0.04)	38.31 (0.18)	38.27 (0.17)*	38.22 (0.15)*	38.21 (0.13)*	37.89 (0.12)*	37.82 (0.10)*	37.81 (0.09)*	37.80 (0.08)*	37.55 (0.09)*	37.52 (0.09)*	37.54 (0.07)*	37.53 (0.07)*	37.36 (0.08)*
Tes (°C)	NH	36.86 (0.09)			36.81 (0.09)	36.90 (0.08)	36.86 (0.08)	36.83 (0.08)	36.81 (0.09)	36.92 (0.09)	36.88 (0.08)	36.82 (0.08)	36.82 (0.08)	36.91 (0.08)	36.87 (0.08)	36.83 (0.08)
	EIH	36.90 (0.08)	40.20 (0.04)	37.57 (0.05)	37.54 (0.05)	37.60 (0.06)	37.63 (0.06)	37.40 (0.07)	37.37 (0.07)	37.46 (0.08)	37.45 (0.08)	37.25 (0.07)	37.22 (0.07)	37.31 (0.07)	37.30 (0.08)	37.10 (0.08)

Data reported or n=8, mean and standard error (±). Asterisk (*) denotes difference from NH, non-exercise/non-heat stress and EIH, exercise-induced hyperthermia. All significance at an alpha level of 0.05.

Table 2. Baroreceptor sensitivity during a repeated orthostatic challenge under a non-exercise/non-heat stress state and following exercise-induced hyperthermia.

Measure	Day	Baseline	HUT1	SUP1	HUT2	SUP2	HUT3	SUP3
BRS ($ms \cdot mmHg^{-1}$)	NH	20.58 (4.73)	8.10 (1.58) †	20.10 (2.46)	8.85 (1.45) †	21.41 (4.10)	9.02 (1.35) †	22.95 (3.53)
	EIH	19.15 (2.63)	1.91 (0.32)* †	8.96 (1.80) *	3.85 (0.44) * †	10.11 (1.95) *	3.43 (0.46) * †	16.69 (3.73) *

Data reported or n=8, mean and standard error (±). BRS, baroreceptor sensitivity; HUT, 70° head-up tilt; SUP, supine. *, denotes difference between NH, non-exercise/non-heat stress and EIH, exercise-induced hyperthermia conditions. †, denotes difference from prior supine position on that day. All significance at an alpha level of 0.05.

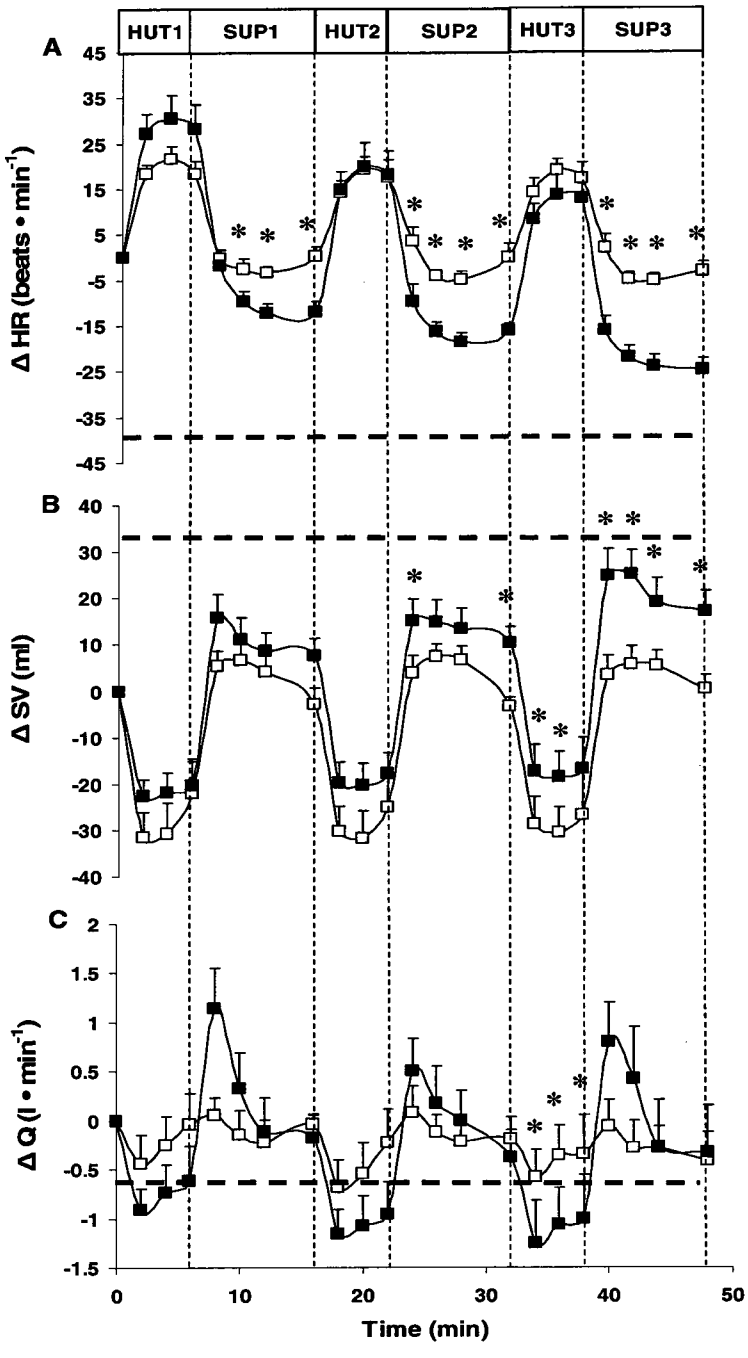

Figure 1. Changes from baseline in heart rate (HR, panel A), stroke volume (SV, panel B), and cardiac output ($\dot{Q}$, panel C) as a function of time during NH (□) or EIH (■). Values are means ± SE. Significant difference between days is denoted by an asterisk (*). The last min of supine resting prior to the repeated postural challenge was used as the baseline value on both days. Pre-exercise resting values for EIH is represented by (--).

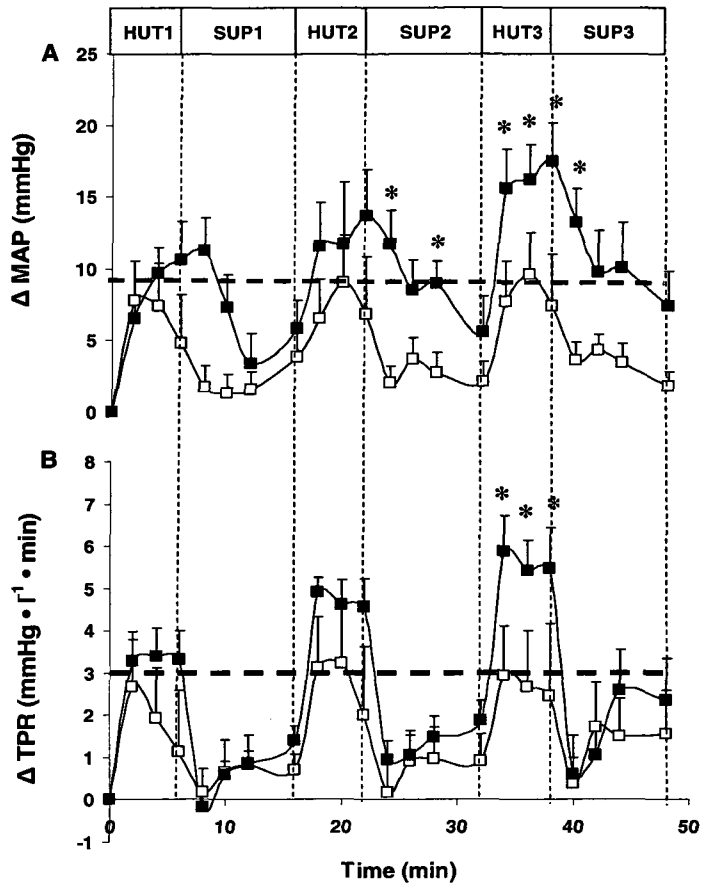

Figure 2. Changes from baseline in mean arterial pressure (MAP, panel A), and total peripheral resistance (TPR, panel B) as a function of time during NH (□) or EIH (■). Values are means ± SE. Significant difference between days is denoted by an asterisk (*). The last min of supine resting prior to the repeated postural challenge was used as the baseline value on both days. Pre-exercise resting values for EIH is represented by (--).

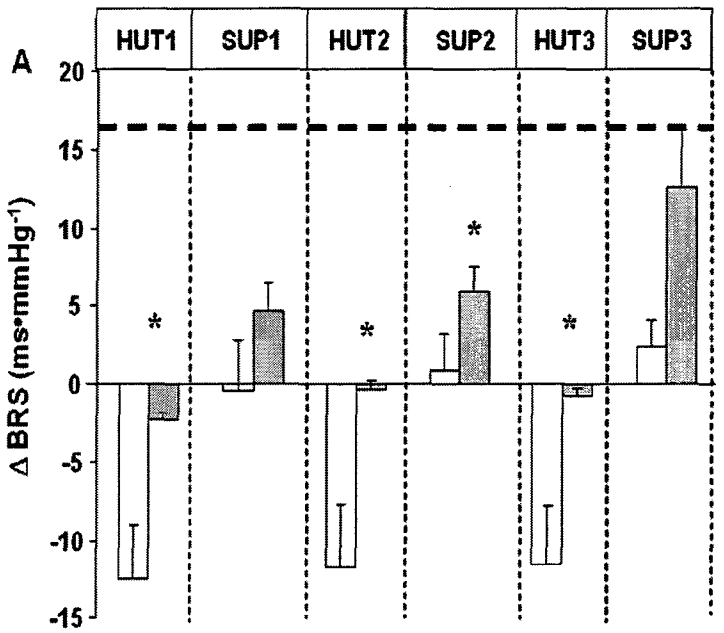

Figure 3. Changes from baseline in baroreceptor sensitivity (BRS, panel A) during repeated postural stress during NH or EIH. Values are means ± SE. Significant difference between days is denoted by an asterisk (*). The last min of supine resting prior to the repeated postural challenge was used as the baseline value on both days. Pre-exercise resting values for EIH is represented by (--).

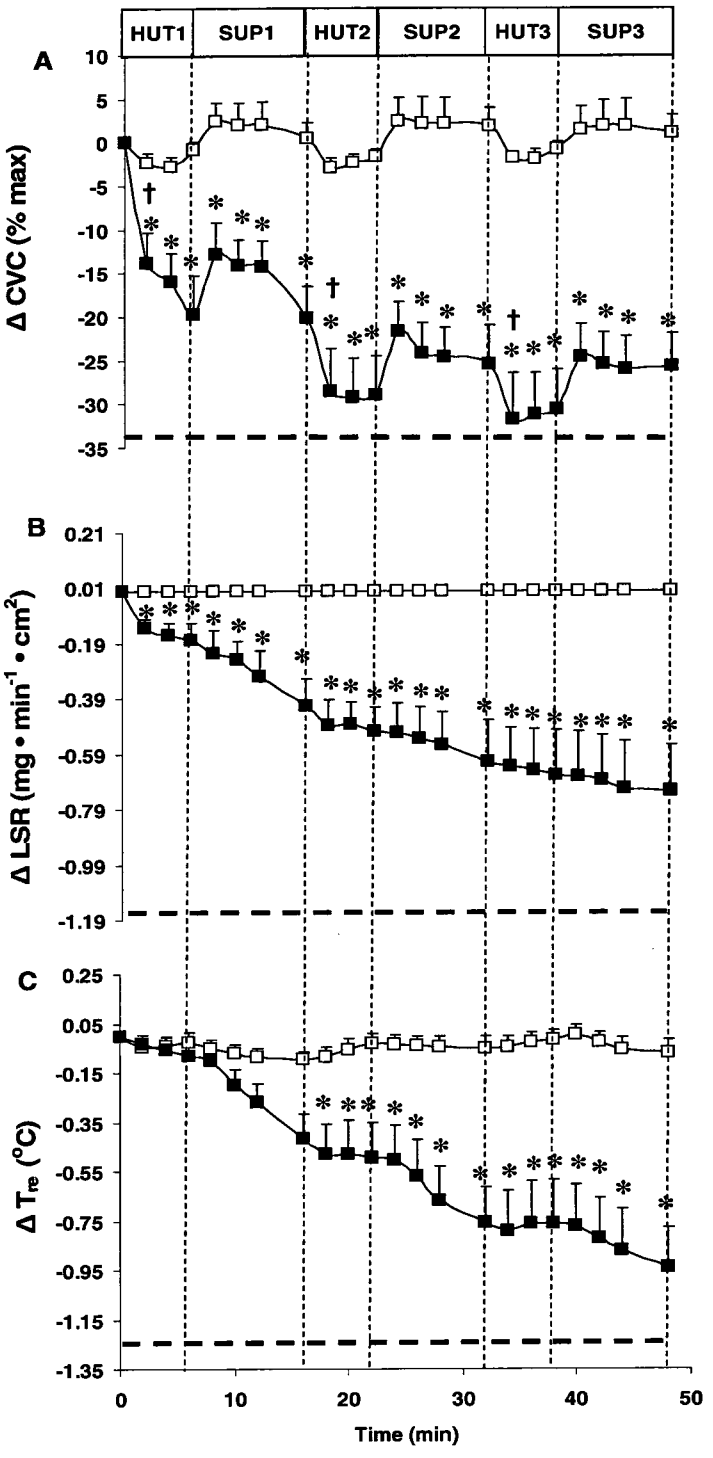

Figure 4. Changes from baseline in forearm cutaneous vascular conductance (%CVC, panel A), upper back sweat rate (panel B), and rectal temperature (panel C) as a function of time during NH (□) or EIH (■). Values are means ± SE. Significant difference between days is denoted by an asterisk (*). (†) denotes difference from prior supine position during EIH. The last min of supine resting prior to the repeated postural challenge was used as the baseline value on both days. Pre-exercise resting values for EIH is represented by (--).

ARTICLE II:

Autonomic nervous system function following exercise-induced hyperthermia

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ABSTRACT

This study was conducted to evaluate the short and long-term recovery pattern of the autonomic nervous system following exercise-induced hyperthermia. Subjects performed orthostatic challenges under non-heat stress, following exercise-induced heat-stress, and at 24 and 48-h postexercise. Participants were exposed to three successive 6-min 70° head-up tilts (HUT1, HUT2 and HUT3), each separated by 10-min supine resting. During the heat-stress trial prior to orthostatic stress, subjects were rendered hyperthermic (rectal temperature ≥39.5°C) by exercise in heat (air temperature (T_{am}) of 42°C) and were subsequently transferred to a T_{am} of 22 °C. Baroreceptor sensitivity (BRS) values were averaged over the last 2 min of each postural position and heart rate variability (HRV) measurements were averaged over the entire duration of each posture. Mean arterial pressure (MAP), total peripheral resistance (TPR), heart rate (HR), cardiac output ($\dot{Q}$) and stroke volume (SV) were evaluated at baseline and at the last min prior to a change in posture. Values following exercise-induced heat-stress, 24 and 48-h were expressed as a change from the non-heat stress control trial. Exacerbated reductions in the ΔBRS and ΔHRV were observed following the short-term (<80-min) recovery period from exercise-induced heat-stress compared to the non-heat stress control trial ($p \leq 0.05$). Normal changes in BRS and HRV to orthostatic stress were re-established following 24-h of recovery. However, greater ΔMAP was observed following 24-h of recovery compared to non-heat stress ($p \leq 0.05$). We conclude that while exercise-induced hyperthermia acutely reduces ANS function the cardiovascular system is able to preserve mean arterial pressure during repeated orthostatic challenges.

Key words: thermoregulation, postural stress, exercise, heart rate variability, cardiovascular

INTRODUCTION

It is well documented that the autonomic nervous system (ANS) plays a key role in the regulation of cardiovascular function during and following a dynamic bout of exercise (Maciel *et al.*, 1986; Iellamo, 2001; Parekh & Lee, 2005). Heart rate variability (HRV), the amount of heart rate fluctuations around the mean heart rate, can be used as a reflection of the cardiorespiratory control system providing information regarding the balance between sympathetic and parasympathetic function of the ANS (van Ravenswaaij-Arts *et al.*, 1993). The attenuation in HRV has been documented during acute and chronic illness (Goldberger *et al.*, 2002) and aging (Ferrari, 2002; Goldberger *et al.*, 2002). Although other factors are likely present in the mitigation of decreased variability (i.e., structural and functional modifications of receptors, vascular/cardiac cell walls that accommodate the receptor units, the respective central or efferent neural pathways, and/or the responsiveness of the effector organ) (Ferrari, 2002), change in autonomic modulation has been regarded as a major determinant. In addition to HRV, baroreceptors are pressure sensors of the ANS (Samniah *et al.*, 2004) that respond to changes in blood pressure by initiating appropriate cardiovascular responses. Baroreceptor sensitivity is attenuated when sympathetic nervous system activity is enhanced and when central arterial compliance is reduced (Skrapari *et al.*, 2007). Insight into baroreflex behaviour is of clinical relevance, since an attenuated baroreflex represents a negative prognostic factor in cardiovascular diseases (Skrapari *et al.*, 2007).

Independent factors such as exercise, heat exposure and/or orthostatic challenges are known to affect ANS function. However, each of these factors has been shown to modulate resting ANS function in different ways. Specifically, exercise has been

demonstrated to cause reductions in BRS (a measure of reflex cardiac vagal responsiveness) (Loimaala *et al.*, 2000) during the short-term recovery period after exercise (~60 min) (Niemela et al., 2008; Ogoh *et al.*, 2005; Skrapari *et al.*, 2007). In addition, studies examining HRV immediately after acute endurance exercise (≤ 30 min) demonstrate an attenuated cardiac vagal modulation and/or a sympathetic predominance during this period (Parekh & Lee, 2005). The decreased variability after exercise demonstrates ANS alterations attributed to a sustained overactivity of the efferent sympathetic nervous system. Furthermore, passive heat exposure resulting in an increase in core temperature (i.e., sublingual temperature increase of 0.5°C) has been demonstrated to induce an activation of the sympathetic nervous system and a withdrawal of the parasympathetic nervous system after 30 min (Yamamoto *et al.*, 2007). Orthostatic stress alters ANS function such that the sensitivity of the cardiac baroreflex in the time domain decreases with increasing tilt angle (i.e., from -20° to +90°) (Westerhof *et al.*, 2006), with a reduction in vagal modulation reported during transient from supine resting to 70° HUT (Iellamo, 2001). While each of these different stimuli (i.e., exercise, hyperthermia and orthostatic stress) are known to modulate ANS function, the combined effects of these stressors remains unknown especially under conditions of elevated thermal strain.

Thermal strain is accompanied by high levels of cardiovascular strain and an impairment of blood pressure and/or critical levels of blood flow to the brain and splanchnic tissues (Cheung, 2007). During exercise, cerebral temperature is known to rise in parallel with core temperature (Nybo, 2008). The development of central nervous system fatigue and subsequent physical exhaustion coincides with the attainment of a

critical core temperature (~40°C) during exercise. Elevated central brain temperature has been shown to have a modulating effect on motor activity (Cheung, 2007; Nybo, 2008). While studies eliciting hyperthermia via exercise in the heat have generally supported a dominant central impairment of neuromuscular activation, the impact on visceral motor (involuntary) activity of the ANS remains unclear.

Numerous studies have shown that exercise-induced hyperthermia can have profound effects on thermal (i.e., attenuated skin blood flow and sweating despite sustained elevations in core temperature) and cardiovascular control (i.e., postexercise hypotension) during the early stages (60-90 min) following cessation of exercise (Kenny *et al.*, 2003; Kenny *et al.*, 2006). However, the link between cardiovascular and thermodynamic control on ANS function following exercise-induced hyperthermia has yet to be resolved especially at elevated levels of hyperthermia. Moreover, it is unclear if this postexercise disturbance in thermal and cardiovascular homeostasis associated with exercise in the heat can pose prolonged effects on ANS function to orthostatic stress at 24 and 48-h postexercise. Exercise is known to elicit a persistent reduction in mean arterial pressure lasting nearly 2 hours in healthy normotensive individuals and as long as 12 hours in hypertensive patients and is further exacerbated by increasing levels of thermal stress (Halliwill, 2001). While a lack of research exists on the long-term recovery pattern of ANS function, investigators have reported attenuations in HRV (a decreased vagal modulation of the heart) for up to 24-h after exhaustive exercise regimens (Furlan *et al.*, 1993; Bernardi *et al.*, 1997; Hautala *et al.*, 2001).

Therefore, the purpose of the present study was to examine the effect of exercise-induced hyperthermia on ANS function during repeated orthostatic challenges in the

early stages of recovery and at 24 and 48-h postexercise. We postulate that the short-term adjustments in BRS and HRV following exercise-induced hyperthermia would present beyond the 24-h postexercise period but not up to 48-h postexercise. By using HRV analysis we were able to supplement our BRS findings with specific data on the individual contributions of the parasympathetic and sympathetic nervous system during recovery from hyperthermia.

METHODS

Participants

Following approval of the experimental protocol from the University of Ottawa Research Ethics Committee, 8 healthy (no history of respiratory, metabolic or cardiovascular disease) and physically active males participated in the study. Body adiposity and peak oxygen consumption ($\dot{V}O_{2peak}$) were measured a minimum 48 h before the experimental trials. The hydrostatic weighing technique was used to determine body density and calculation of the percentage of body fat was used based on the Siri equation (Siri, 1956). Peak oxygen consumption was measured during a progressive treadmill running protocol and the data were used to select the submaximal workload (~65% of $\dot{V}O_{2peak}$) for the experimental exercise phase of the study. Participants characteristics were as follows: aged (22 ± 3 yrs), height (177 ± 4 cm), weight (73 ± 6 kg), body surface area (1.89 ± 0.09 m^2), body fat (14.6 ± 5 %), and $\dot{V}O_{2peak}$ (62.8 ± 7.2 $ml \cdot kg^{-1} \cdot min^{-1}$).

Measurements

Rectal temperature (T_{re}) was monitored continuously using a pediatric thermocouple probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical, St-Louis, MO, USA) inserted 12 cm past the anal sphincter. Esophageal temperature (T_{es}) was measured by placing a pediatric thermocouple probe of approximately 2 mm in diameter (Mon-a-therm Nasopharyngeal Temperature Probe, Mallinckrodt Medical, St-Louis, MO, USA) through the participant's nostril while they were asked to sip water through a straw. The location of the probe tip in the esophagus was estimated to be at the level of the eighth and ninth thoracic vertebrae.

Heart rate (HR) was monitored using a Polar coded transmitter, recorded continuously and stored with a Polar Advantage interface and Polar Precision Performance software (Polar Electro Oy, Finland).

Mean arterial pressure (MAP), cardiac output ($\dot{Q}$), and baroreceptor sensitivity (BRS) were estimated from the integration of a non-invasive recording of blood pressure at the middle digit of the right hand (Finapres 2300, Ohmeda, Madison, WI, USA) fixed at heart level (the third intercostal space). MAP was also verified periodically throughout the protocol by auscultation of the brachial artery. Stroke volume (SV) was calculated as $\dot{Q}$/HR. Total peripheral resistance (TPR) was calculated as MAP/$\dot{Q}$. For BRS, the Beatfast software (BeatScope 1.1a, Amsterdam, The Netherlands) was used to determine beat-to-beat variables, interbeat interval (IBI) and systolic, diastolic, and mean arterial pressures. Systolic blood pressure and IBI were used to calculate BRS in $mm \cdot mmHg^{-1}$ (Westerhof *et al.*, 2006).

Heart rate variability (HRV) was estimated from RR interval data collected from a 5-lead electrocardiogram (ECG) (DigiTrak Plus Recorder, Andover MA). HRV analysis was performed with *continuous individualized variability analysis* (CIMVA) software that performs multi-parameter characterization of variability (including time-domain, frequency-domain, scale-invariant and complexity measures of variability) (Seely & Macklem, 2004). However, only time and frequency domain metrics were computed to limit our analysis to physiological measures of ANS function. CIMVA software performs artifact detection and elimination to ensure each variability measure is reliable and accurate (Seely & Macklem, 2004). Poor quality signals are not processed by the CIMVA core and annotated as bad signal (Seely & Macklem, 2004). Time-domain measures of HRV were calculated from the time series of interbeat intervals: mean interbeat interval (RR), standard deviation of RR intervals (SDRR), and root mean squared standard deviation of RR intervals (rMSSD). Fast Fourier Transform frequency-domain measures of HRV provide an index of autonomic balance by separating the cyclical variations in heart rate into those occurring at high-frequencies (HF) (0.18-0.4 Hz) which appear to be the result of vagal modulation, and those occurring at low-frequencies (LF) (0.04-0.15) which are reported to reflect both sympathetic and vagal modulation. In addition, the ratio of low- to high-frequency (LF:HF) components has been proposed as a measure of cardiac sympatho-vagal balance (Seely & Macklem, 2004; Parekh & Lee, 2005). Maximal Overlap Discrete Wavelet Transform (DWT) of HRV was computed by transforming RR interval signal to time-frequency domain (Seely & Macklem, 2004).

A Teeter Hang Ups F5000 inversion table was used to manipulate posture. The angle of the tilt was measured using a Unitek Magnetic Polycast Protracter.

Experimental protocol

Subjects were instructed to avoid physical activity and excessive stressors such as exposure to hot or cold temperatures, particularly during the period between awakening and experimentation and during transit from home to the laboratory. Trials were performed at the same time of day for each subject to avoid circadian variation in core and skin temperatures. Subjects were asked to fast at least 2 h prior to experimentation, and water ingestion was permitted *ad libitum* during this time to promote euhydration. However, water consumption was restricted at the start of the experimental trial. On arrival at the laboratory for each experimental trial, subjects clothed in shorts and athletic shoes were fitted with the appropriate instruments.

Each subject performed four experimental trials. During the first experimental session, subjects remained resting in the supine posture for 30 min in a non-heat stress ambient temperature of 22°C. At the end of the baseline period, subjects were exposed to three consecutive 6-min 70° head-up tilts (HUT1, HUT2 and HUT3 respectively), separated by a 10-min supine recovery (i.e., SUP1, SUP2 and SUP3 respectively). During the second experimental trial, subjects remained resting in the supine position for 30-min. At the end of the baseline resting period, subjects entered an adjoining temperature-controlled chamber maintained at 42°C where they performed treadmill running at about 65% of their predetermined $\dot{V}O_{2peak}$ until rectal temperature reached 39.5°C (24 ± 5 min). Immediately following the cessation of exercise, the participants were transferred back to a non-heat stress ambient temperature of 22°C where they remained seated in an upright posture for ~15 min. This was done to ensure that core temperature achieved a stable elevated value paralleled by a reduction in skin perfusion

and sweating to resting baseline values prior to the start of the postural stress (Kenny *et al.*, 2007). They were then placed on a tilt-table in a supine posture for 15-min and subsequently exposed to three consecutive 6-min 70° HUT, separated by 10 min recovery in the supine posture.

The third and fourth experimental sessions took place 24 and 48 hours after the second experimental session performed under non-heat stress conditions (ambient temperature of 22°C). During this time participants were instructed to refrain from physical activity, alcohol, caffeine and any excessive stressors such as exposure to hot or cold temperatures. The design was the same as the first experimental session.

Statistical analyses

A one-way repeated measures analysis of variance (ANOVA) was used to analyze the baseline values for each variable between days. For BRS, values were averaged over the last 2 min of each postural position and HRV values were averaged over the entire duration of each period. The non-heat stress condition was used as the baseline control trial; such that responses in the dependent variables on subsequent days were compared to the non-heat stress condition. Therefore, for each cycle of head-up tilt and supine recovery, a two-way repeated measures ANOVA was used to analyze the changes in BRS, HRV (DWT, HF, LF, and LF:HF), Mean RRI, SDRRI, rMSSD, HR, MAP, TPR, SV, $\dot{Q}$, T_{es} using the repeatable factors of experimental session (levels: non-heat stress, postexercise heat-stress, 24-h and 48-h), and postural position (levels: HUT1, HUT2, HUT3, SUP1, SUP2 and SUP3). Absolute values can be found in tables 1-4. Pair-wise comparisons were performed using paired sample t-tests. The level of significance was

set at 0.05 and the alpha level was adjusted during multiple comparisons so as to maintain the rate of type I error at 5% during Holm-Bonferroni post-hoc analysis. All analyses were performed using the statistical software package SPSS 17.0 for Windows (SPSS Inc. Chicago, IL, USA).

RESULTS

Prior to postural manipulation, there was no significant difference between days for absolute baseline values of BRS, HRV (DWT), LF:HF power, HF power and LF power as well as the hemodynamic responses ($p>0.05$).

Autonomic nervous system function

ΔBRS. During repeated postural changes, ΔBRS remained constant over successive postural positions in both the HUT ($p=0.605$) and SUP ($p=0.431$) positions for all trials. ΔBRS was significantly different between trial days ($p \leq 0.05$); such that ΔBRS was significantly reduced postexercise compared to the non-heat stress control trial in HUT1, HUT2, HUT3, SUP1, SUP2 & SUP3 ($p \leq 0.05$) (Fig. 1).

***ΔHRV* (DWT).** The relative % change in HRV increased over successive postural positions in HUT ($p \leq 0.05$), but remained constant over successive SUP ($p=0.56$) positions. ΔHRV was significantly different between trial days in HUT and SUP ($p \leq 0.05$); such that ΔHRV was significantly reduced postexercise compared to the non-heat stress control trial in HUT1, HUT2, HUT3, SUP1, SUP2 & SUP3 ($p \leq 0.05$) (Fig. 2).

ΔLF:HF. The relative % change in LF:HF remained constant over successive postural positions in both the HUT (p=0.238) and SUP (p=0.109) positions for all trials. ΔLF:HF was not significantly different between trial days in HUT (p=0.088), but was significantly different between trial days in SUP ($p \leq 0.05$); such that ΔLF:HF was significantly elevated postexercise compared to the non-heat stress control trial in SUP1 & SUP2 (Fig. 3).

ΔHF. The relative % change in HF power remained constant over successive postural positions in HUT (p=0.662), but increased over successive postural positions in SUP ($p \leq 0.05$). However, ΔHF power was significantly different between trial days in HUT and SUP ($p \leq 0.05$); such that ΔHF was significantly reduced postexercise compared to the non-heat stress control trial in HUT1, HUT2, HUT3, SUP1, SUP2 & SUP3 ($p \leq 0.05$) (Fig. 3).

ΔLF. The relative % change in LF power remained constant over successive postural positions in both the HUT (p=0.616) and SUP (p=0.663) positions for all trials. However, ΔLF power was significantly different between trial days in HUT and SUP ($p \leq 0.05$); such that ΔLF was significantly reduced during postexercise compared to the non-heat stress control trial in HUT1, HUT2, HUT3, SUP1, SUP2 and SUP3 ($p \leq 0.05$) (Fig. 3).

Hemodynamic Responses

ΔMAP. The relative ΔMAP remained constant over successive postural positions in both the HUT (p=0.521) and SUP (p=0.230) positions for all trials. ΔMAP was significantly different between trial days in HUT and SUP ($p \leq 0.05$); such that ΔMAP

was significantly elevated 24-hr postexercise compared to the non-heat stress control trial in HUT1, HUT2, HUT3 & SUP2. ΔMAP was significantly reduced postexercise compared to the non-heat stress control trial in SUP2.

ΔTPR. During postural changes, ΔTPR remained constant over successive postural positions in both the HUT (p=0.980) and SUP (p=0.953) positions for all trials. ΔTPR was not significantly different between trials in HUT (p=0.402). In the supine position, ΔTPR was significantly different between trials ($p \leq 0.05$); such that ΔTPR was significantly reduced postexercise compared to the non-heat stress control trial in SUP1 ($p \leq 0.05$) (Table 3).

ΔHR. During postural changes, ΔHR decreased over successive postural positions in HUT ($p \leq 0.05$), but remained constant over successive SUP (p=0.713) positions. ΔHR was significantly different between trial days in HUT and SUP ($p \leq 0.05$); such that ΔHR was significantly elevated postexercise compared to the non-heat stress control trial in HUT1, HUT2, HUT3, SUP1, SUP2 and SUP3 ($p \leq 0.05$) (Table 3).

ΔSV. During postural changes, ΔSV remained constant over successive postural positions in both the HUT (p=0.204) and SUP (p=0.839) positions for all trials. ΔSV was significantly different between trial days in HUT and SUP ($p \leq 0.05$); such that ΔSV was significantly reduced postexercise compared to the non-heat stress control trial in HUT1, HUT2, HUT3, SUP1, SUP2 and SUP3 ($p \leq 0.05$) (Table 3).

$\Delta \dot{Q}$. During postural changes, $\Delta \dot{Q}$ r remained constant over successive postural positions in both the HUT (p=0.947) and SUP (p=0.535) positions for all trials. $\Delta \dot{Q}$ was not significantly different between trials in HUT (p=0.965). $\Delta \dot{Q}$ was significantly

different between trials in SUP ($p \leq 0.05$); such that $\Delta \dot{Q}$ was significantly elevated postexercise compared to the non-heat stress control trial in SUP1 ($p \leq 0.05$) (Table 3).

DISCUSSION

In the following study, we examined the interplay between thermal and nonthermal stimuli measured during repeated 70° head-up tilts (used to modify baroreceptor loading status) performed during the early (first 80 min of recovery) and late-stages (24 and 48-h) following exercise induced-hyperthermia. By comparing responses under a non-heat stress condition, we show that exercise-induced hyperthermia (esophageal temperature of $\geq 40.0^{\circ}C$) exacerbates reductions in ANS function. We observed a sustained elevation of core temperature which was paralleled by a significant hypotension. This apparent perturbation in postexercise thermoregulatory control has been ascribed to nonthermal baroreceptor input associated with a postexercise hypotension response (Kenny *et al.*, 2007). Our findings suggest that a link does indeed exist between cardiovascular and thermoregulatory control following exercise-induced hyperthermia as evidenced by the parallel attenuations in MAP and both BRS and HRV during the repeated orthostatic challenge. While it is evident from our findings that the acute disturbances in postexercise thermal and cardiovascular homeostasis are influenced by changes in ANS function during the early stages of exercise recovery, a normal pattern of response in ANS function and cardiovascular control to a repeated orthostatic challenge was re-established after a 24-h recovery period. However, a greater relative change in MAP was observed during repeated orthostatic challenges following 24-h of recovery as compared to the non-heat stress control condition.

ANS function during postural stress following exercise-induced hyperthermia

It is well known that orthostatic stress causes attenuations in BRS and HRV (Butler *et al.*, 1994; Iellamo, 2001; Westerhof *et al.*, 2006). Specifically, healthy subjects during postural stress from supine to 70° HUT in thermoneutral ambient conditions experience a reduction in BRS (Iellamo, 2001; Westerhof *et al.*, 2006). In addition to orthostatic stress, BRS has been reported to remain attenuated during the short-term recovery period after exercise for ~60 min in thermoneutral conditions (Terziotti *et al.*, 2001; Ogoh *et al.*, 2005; Niemela *et al.*, 2008). Until the present study, it was unclear how the combination of orthostatic stress presented following exercise-induced hyperthermia affects ANS function.

We show that following exercise-induced heat stress, BRS was reduced prior to the orthostatic stress from 19 ± 3 ms·mmHg^{-1} at baseline to 4 ± 0.4 ms·mmHg^{-1} prior to HUT1. This attenuation in BRS persisted throughout the short-term recovery period and was paralleled by a sustained elevation in core temperature. Consistent with previous studies, we observed a reduction in BRS during the postural stress (i.e., 70° HUT) (Westerhof *et al.*, 2006). However, we show that the magnitude of the reduction was less following exercise-induced hyperthermia as compared to non-heat stress control (Table 1). The reduction in the range of responsiveness of the baroreflex supports previous suggestions that heat-stress induced reductions in orthostatic tolerance may be an indication that hyperthermia reduces the range in which baroreflexes can increase sympathetic activity during a hypotensive challenge (Crandall, 2008). We show that the restoration of baseline MAP and core temperature throughout exercise recovery was paralleled by a concomitant increase in BRS. The primary neural structures governing

thermoregulation are located in the hypothalamus, and electrical stimulation of the hypothalamus is known to modify baroreceptor activity (Crandall *et al.*, 2000). The capacity of nonthermal baroreceptor reflexes to override thermoregulatory input during hyperthermia is critical to maintain blood pressure. However, this can significantly compromise heat loss (Kenny *et al.*, 2006; Kenny *et al.*, 2007). This is a reasonable linkage given that there is some hypothalamic control over baroreflex function (Gebber & Snyder, 1970).

Changes in HRV are known to occur during postural stress such that with greater levels of HUT, HRV is reduced (Butler *et al.*, 1994). Specifically, a decrease in high-frequency power has been previously reported during postural transition from supine resting to 70° HUT (Iellamo, 2001). In addition to orthostatic stress, HRV measures have been suggested to return to near-baseline levels within 30-min postexercise in thermoneutral conditions (Terziotti *et al.*, 2001; Parekh & Lee, 2005). Analysis of HRV has demonstrated a depressed high-frequency power and/or increased low to high-frequency ratio after exercise at intensities ranging from 50% of estimated peak power output to maximal exertion (Parekh & Lee, 2005). In the present study, exercise-induced hyperthermia reduced HRV prior to postural stress performed in thermoneutral conditions thereby exacerbating the reduction in HRV during the repeated orthostatic challenge compared to the non-heat stress control condition. HRV was reduced by 76 ± 14 % in HUT1 following exercise-induced hyperthermia and remained attenuated throughout the <80-min recovery period (Fig. 2). We show a reduction in HRV of 31 ± 9 % during the last supine position postexercise (Fig. 2). A longer duration of time (>80-min compared to previously reported 30-min duration until restoration of normal cardiac autonomic

balance) was needed to restore measures of HRV following exercise heat stress compared to previous research findings on endurance exercise performed in a non-heat stress condition (Terziotti *et al.*, 2001; Parekh & Lee, 2005). Specifically, during the early stages of exercise recovery high-frequency power was significantly reduced by 66 ± 6 % in HUT1 as compared to the non-heat stress control condition (Fig. 3). High-frequency power remained attenuated throughout the short-term recovery period demonstrating attenuated cardiac vagal activity for <80-min following exercise-induced hyperthermia. However, sympathovagal balance was maintained following exercise-induced hyperthermia (Fig. 3). Therefore, the additional cardiovascular strain imposed during exercise-induced hyperthermia exacerbated the recovery of vagal reactivation previously shown to occur during exercise in thermoneutral conditions. Since a delay in vagal reactivation following exercise has been implicated in the development of dangerous arrhythmias (Parekh & Lee, 2005), our findings demonstrate the importance of using HRV measures when recommending safe periods of recovery following exercise and/or activity in the heat.

We show that reductions in core temperature by 80-min post-exercise were paralleled by restorations in the sensitivity of the baroreflex and variability of heart rate. Several investigators have reported that the thermoregulatory control system alters arterial blood pressure, inducing spontaneous oscillation characteristics, such as HRV (Akselrod *et al.*, 1981; Kitney, 1971). It is clear from our results that exercise-induced hyperthermia has a profound effect on postexercise BRS and HRV responses and when combined with postural stress the effect is exacerbated. As such, under conditions of

continued heat exposure and/or postural/gravitational stress this may lead to a compromised cardiovascular function leading to heat and/or postural induced syncope.

ANS function following 24 and 48-h of recovery

We show that changes in BRS and HRV throughout postural stress are not significantly different after 24-h of exercise recovery compared to values reported during the non-heat stress control condition. Despite reductions in BRS and HRV during the short-term recovery period after exercise in the heat, the re-establishment of these variables by 24-h coincided with the return of core temperature and hemodynamic measures to baseline resting values. It appears as though the ANS is able to restore normal response to postural stress following 24-h recovery after the removal of an exercise stimulus and/or hyperthermia. Our findings are in disagreement with previous investigators who have reported attenuations in HRV (as evidence by a decreased vagal modulation of the heart) for up to 24-h after prolonged exhaustive exercise (Furlan *et al.*, 1993; Bernardi *et al.*, 1997; Hautala *et al.*, 2001). It is possible that although we induced large elevations in core temperature during exercise (average increase in esophageal temperature of 3.3°C), the duration of our exercise protocol (~25 min) may have been insufficiently long to elicit reductions in ANS function for upwards of 24-h. Further studies are required to examine the interplay between the exercise-induced hyperthermia and central nervous system fatigue (typically observed with prolonged exhaustive exercise) on ANS function.

A novel observation of this study was the observed greater relative change in MAP during orthostatic stress measured following 24-h. In contrast to the response

measured during the non-heat stress control condition, we show that the increase in the change in MAP was the product of both an increase in systolic and diastolic blood pressure. For example at the final HUT (i.e., HUT3), systolic and diastolic blood pressure averaged 139 ± 7 mmHg and 89 ± 3 mmHg respectively. This response was paralleled by a slight increase in TPR following 24-h of recovery. Orthostatic hypertension has previously been classified by an increase in blood pressure upon assumption of upright posture (Fessel & Robertson, 2006) by either an increase in diastolic blood pressure from <90 mmHg to ≥90 mmHg, an increase in systolic blood pressure from <140 mmHg to ≥140 mmHg (Yoshinari *et al.*, 2001) or an overall increase in systolic blood pressure by at least 20 mmHg (Fessel & Robertson, 2006). Our systolic and diastolic blood pressure results meet the cut-off values for clinical diagnosis of orthostatic hypertension. The significantly greater change in MAP cannot be explained by changes in BRS and/or HRV as these values were restored to baseline resting values. Therefore, other factors likely contributed to increases in arterial blood pressure following 24-h of recovery. It is plausible that the significant loss of body water and electrolytes (average loss of body weight ~1.2 kg) associated with elevated sweat rates during and following exercise in the heat lead to dehydration and hyperosmolarity (Bartholomew *et al.*, 2005; Nybo, 2008). Exercise is known to cause an acute loss of plasma volume that is restored within 60-minutes of exercise cessation even in the absence of fluid ingestion (Lundvall & Lanne, 1989; Gillen *et al.*, 1991). This fluid-flux into the vascular space from other fluid pools, notably the lymph (Nagashima *et al.*, 2001) has been suggested to occur due to alterations in Starling forces, elevations in plasma albumin mass and plasma osmolarity (Nose *et al.*, 1988). The restoration of

plasma volume reportedly increases to a greater extent compared to the original (pre-exercise) plasma volume, and is retained at 24-h postexercise resulting in the phenomenon of exercise-induced hypervolemia (Bartholomew *et al.,* 2005; Gillen *et al.*, 1991; Nagashima *et al.*, 1999; Nagashima *et al.*, 2001). The exercise-induced hypervolemia may be further enhanced by increased renal sodium and water retention in the 24-hours following exercise, potentially as a consequence of an increase in aldosterone concentration (Nagashima *et al.*, 1999; Nagashima *et al.*, 2001) or reciprocally, a decrease in atrial natriuretic peptide concentration (Hanel *et al.*, 1997). While we did not directly measure plasma volume concentrations, our findings are consistent with previous research and warrant further investigation into the specific contributions of hyperthermic exercise on plasma volume restoration and possible hypervolemia compared to exercise performed in thermoneutral conditions.

Summary

We conclude that exercise-induced hyperthermia causes a short-term depression in BRS and HRV which is exacerbated by postural stress. Our data provides valuable new insight relating to the role of the autonomic nervous system as an important nonthermal factor contributing to the postexercise disturbance of thermal and cardiovascular homeostasis. Indeed, our results show that attenuations in baroreceptor sensitivity and heart rate variability were paralleled by elevations in esophageal temperature as well as significant hypotension that was most pronounced during the early stages of recovery when BRS and HRV were greatly reduced. Of note however, the reduced sensitivity of the baroreflex and variability of heart rate observed in the early

stages following exercise-induced hyperthermia (i.e., <80-min) was not evident following 24-h of recovery.

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Table 1. Baroreceptor sensitivity during repeated 70° head-up tilts performed under a non-heat stress state and in the early and late stages (24 and 48-h) of recovery following exercise-induced hyperthermia.

Variable	Experimental Trial	Pre-exercise	Supine	HUT1	SUP1	HUT2	SUP2	HUT3	SUP3
BRS	NHS	20.6 (4.7)		8.1 (1.6)	20.1 (2.5)	8.9 (1.5)	21.4 (4.1)	9.0 (1.4)	23.0 (3.5)
($ms \cdot mmHg^{-1}$)	EIH	19.2 (2.6)	4.2 (0.4)†‡	1.9 (0.3)*	9.0 (1.8)*	3.9 (0.4)*	10.1 (2.0)*	3.4 (0.5)*	16.8 (3.7)*
	24-h	19.8 (2.1)		8.6 (1.5)	22.7 (3.9)	9.7 (1.3)	22.1 (2.8)	9.2 (1.6)	20.6 (1.5)
	48-h	23.7 (4.6)		9.4 (1.8)	21.4 (2.2)	9.3 (1.8)	21.3 (2.1)	10.3 (1.7)	23.8 (2.4)

Data reported or n=8, mean and standard error (±). Values reported for Supine represent the average of the final 2-min of the 15-min supine resting period prior to HUT1. *, denotes difference from non-heat stress control conditions (NHS). †, denotes difference from pre-exercise baseline resting. ‡, denotes difference from NHS baseline resting. EIH, Exercise-induced hyperthermia. 24-h, indicates responses measured 24-h after EIH. 48-h, indicates responses measured 48-h after EIH. Significance at an alpha level of 0.05.

Table 2. Cardiovascular responses during repeated 70° head-up tilts performed under a non-heat stress state and in the early and late stages (24 and 48-h) of recovery following exercise-induced hyperthermia.

Variable	Experimental Trial	Pre-exercise	End of Exercise	Supine	HUT1	SUP1	HUT2	SUP2	HUT3	SUP3
Mean RR interval	NHS	1.04 (0.15)			0.90 (0.1)	0.95 (0.12)	0.93 (0.1)	0.98 (0.12)	0.93 (0.08)	1.02 (0.11)
	EIH	1.01 (0.11)	0.45 (0.12)†‡	0.58 (0.05)†‡	0.55 (0.07)*	0.64 (0.06)*	0.61 (0.09)*	0.69 (0.06)*	0.63 (0.09)*	0.73 (0.08)*
	24-h	1.06 (0.18)			0.90 (0.13)	0.99 (0.12)	0.96 (0.17)	1.02 (0.13)	0.94 (0.15)	1.04 (0.14)
	48-h	1.06 (0.16)			0.91 (0.14)	0.94 (0.10)	0.93 (0.15)	1.02 (0.12)	0.92 (0.16)	1.06 (0.13)
SDRR interval	NHS	0.09 (0.03)			0.13 (0.04)	0.14 (0.04)	0.14 (0.04)	0.14 (0.04)	0.14 (0.04)	0.15 (0.04)
	EIH	0.10 (0.04)	0.10 (0.09)†‡	0.03 (0.01)†‡	0.04 (0.01)*	0.06 (0.03)*	0.06 (0.03)*	0.07 (0.04)*	0.08 (0.04)*	0.09 (0.05)*
	24-h	0.09 (0.03)			0.12 (0.03)	0.15 (0.07)	0.14 (0.04)	0.15 (0.06)	0.14 (0.05)	0.14 (0.06)
	48-h	0.10 (0.03)			0.14 (0.05)	0.16 (0.06)	0.16 (0.04)	0.17 (0.07)	0.15 (0.05)	0.17 (0.06)
rMSSD	NHS	0.08 (0.04)			0.06 (0.03)	0.07 (0.03)	0.06 (0.03)	0.07 (0.02)	0.06 (0.03)	0.08 (0.03)
	EIH	0.07 (0.04)	0.03 (0.03)†‡	0.01 (0.00)†‡	0.01 (0.00) *	0.02 (0.01)*	0.02 (0.01)*	0.03 (0.02)*	0.02 (0.01)*	0.04 (0.02)*
	24-h	0.07 (0.03)			0.06 (0.03)	0.07 (0.02)	0.07 (0.03)	0.07 (0.02)	0.06 (0.03)	0.07 (0.02)
	48-h	0.07 (0.03)			0.06 (0.03)	0.06 (0.02)	0.06 (0.03)	0.08 (0.02)	0.06 (0.03)	0.08 (0.02)

Data reported or n=8, mean and standard error (±). Values reported for Supine represent the average of the 15 min supine resting period prior to HUT1. *, denotes difference from non-heat stress control conditions (NHS). †, denotes difference from pre-exercise baseline resting. ‡, denotes difference from NHS baseline resting. EIH, Exercise-induced hyperthermia. 24-h, indicates responses measured 24-h after EIH. 48-h, indicates responses measured after 48-h after EIH. SDRR, standard deviation of RR intervals. rMSSD, root mean squared standard deviation of RR intervals. Significance at an alpha level of 0.05.

Table 3. Hemodynamic responses during repeated 70° head-up tilts performed in the early and late stages (24 and 48-h) of recovery following exercise-induced hyperthermia.

Variable	Experimental Trial	Baseline resting	HUT1	SUP1	HUT2	SUP2	HUT3	SUP3
HR	EIH	4 (3)	50 (5)*	28 (4)*	41 (5)*	24 (4)*	36 (5)*	18 (4)*
(beats•min^{-1})	24-h	1 (3)	1 (4)	-1 (3)	-1 (4)	-1 (4)	0 (4)	3 (2)
	48-h	-1 (3)	4 (3)	-2 (3)	2 (3)	-2 (3)	3 (4)	0 (2)
MAP	EIH	-4 (3)	-4 (3)	-7 (4)	-3 (6)	-6 (2)*	1 (5)	-4 (3)
(mmHg)	24-h	0 (3)	8 (3)*	2 (3)	8 (4)*	7 (3)*	8 (4)*	5 (3)
	48-h	-4 (3)	1 (5)	-3 (2)	-1 (4)	-2 (2)	0 (3)	-1 (3)
TPR	EIH	-0.6 (0.7)	-0.8 (1.4)	-2.3 (0.7)*	-0.4 (1.7)	-2.0 (1.1)	0.0 (1.6)	-2.2 (1.6)
(mmHg•l^{-1}•min)	24-h	1.4 (0.7)	0.9 (0.9)	0.6 (0.6)	1.9 (1.5)	0.8 (0.7)	1.1 (1.3)	0.2 (1.0)
	48-h	1.1 (0.9)	0.7 (2.1)	0.1 (0.8)	-1.1 (1.8)	-0.1 (0.9)	-0.2 (1.3)	0.4 (1.2)
SV	EIH	-3 (4)	-32 (4)*	-23 (5)*	-27 (6)*	-20 (2)*	-24 (5)*	-17 (3)*
(ml)	24-h	-7 (4)	1 (7)	2 (3)	-1 (5)	3 (4)	4 (6)	1 (4)
	48-h	-6 (5)	-7 (6)	4 (4)	5 (8)	4 (4)	1 (7)	0 (5)
$\dot{Q}$	EIH	0.1 (0.2)	0.0 (0.3)	0.5 (0.1)*	-0.1 (0.4)	0.4 (0.3)	-0.1 (0.4)	0.7 (0.4)
(l•min^{-1})	24-h	-0.5 (0.1)	0.1 (0.2)	-0.1 (0.2)	-0.2 (0.4)	0.1 (0.3)	0.1 (0.3)	0.3 (0.3)
	48-h	-0.5 (0.2)	-0.2 (0.5)	-0.2 (0.2)	0.3 (0.5)	-0.1 (0.3)	0.1 (0.4)	-0.1 (0.3)

Data reported or n=8, mean and standard error (±).*, denotes difference from non-heat stress control conditions (NHS). EIH, Exercise-induced hyperthermia. 24-h, indicates responses measured 24-h after EIH. 48-h, indicates responses measured 48-h after EIH. HR, heart rate. MAP, mean arterial pressure. TPR, total peripheral resistance. SV, stroke volume. $\dot{Q}$, cardiac output. Significance at an alpha level of 0.05.

Table 4. Esophageal temperature response during repeated 70° head-up tilts performed under a non-heat stress state and in the early and late stages (24 and 48-h) of recovery following exercise-induced hyperthermia.

Variable	Experimental Trial	Pre-exercise	End of Exercise	Supine	HUT1	SUP1	HUT2	SUP2	HUT3	SUP3
T_{es} (°C)	NHS	36.86 (0.09)			36.90 (0.08)	36.83 (0.08)	36.92 (0.09)	36.82 (0.08)	36.91 (0.08)	36.83 (0.08)
	EIH	36.90 (0.08)	40.20 (0.04)†‡	37.57 (0.05)†‡	37.60 (0.06)*	37.40 (0.07)*	37.46 (0.08)*	37.25 (0.07)*	37.31 (0.07)*	37.10 (0.08)*
	24-h	36.66 (0.17)			36.69 (0.15)	36.63 (0.16)	36.74 (0.16)	36.65 (0.17)	36.74 (0.17)	36.64 (0.17)
	48-h	36.79 (0.09)			36.86 (0.10)	36.78 (0.09)	36.86 (0.11)	36.76 (0.09)	36.86 (0.12)	36.75 (0.10)

Data reported or n=8, mean and standard error (±).Values reported for Supine represent the average of the final minute of the 15-min supine resting period prior to HUT1. *, denotes difference from non-heat stress control conditions (NHS). †, denotes difference from pre-exercise baseline resting. ‡, denotes difference from NHS baseline resting. EIH, Exercise-induced hyperthermia. 24-h, indicates responses measured 24-h after EIH. 48-h, indicates responses measured 48-h after EIH. T_{es}, esophageal temperature. Significance at an alpha level of 0.05.

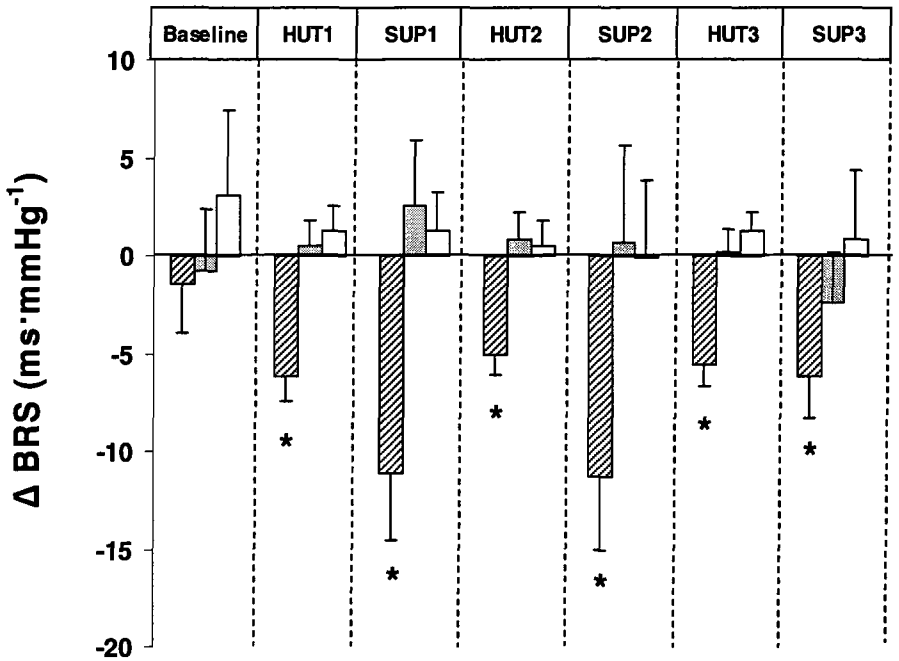

Figure 1. Relative change in baroreceptor sensitivity (△BRS) from the non-heat stress control trial as measured during repeated 70° head-up tilts performed in the early (stripped bars) and late stages [24-hr (grey bars) and 48-h (white bars)] of recovery following exercise-induced hyperthermia. Values are means ± SE. Significant differences between the non-heat stress control trial and postexercise hyperthermia are denoted by (*), $p<0.05$.

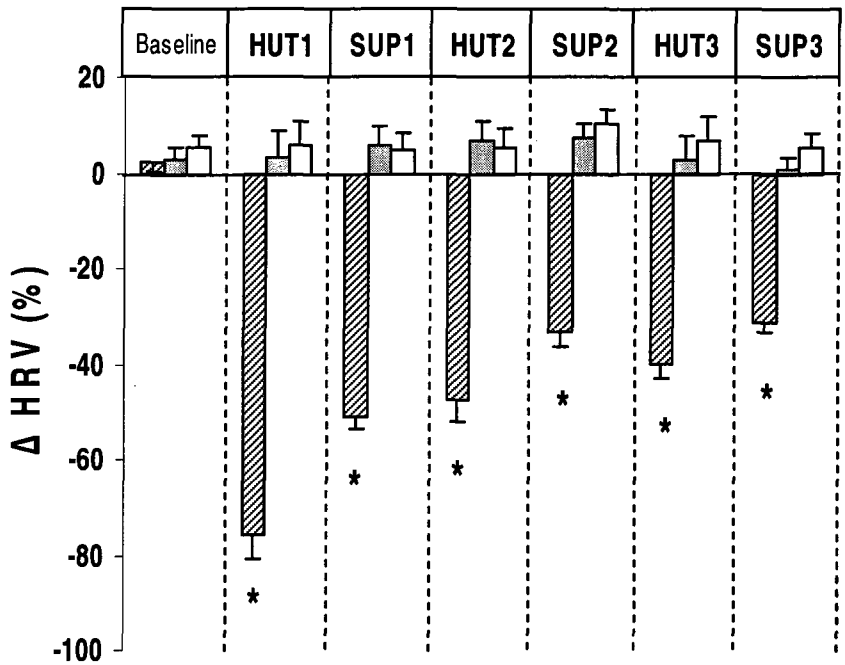

Figure 2. Relative % change in heat rate variability (△HRV) from the non-heat stress control trial as measured during repeated 70° head-up tilts performed in the early (stripped bars) and late stages [24-hr (grey bars) and 48-h (white bars)] of recovery following exercise-induced hyperthermia. Heart rate variability was calculated from the Maximal Overlap Discrete Wavelet Transform. Values are means ± SE. Significant differences between non-heat stress control and postexercise hyperthermia are denoted by an (*), $p<0.05$.

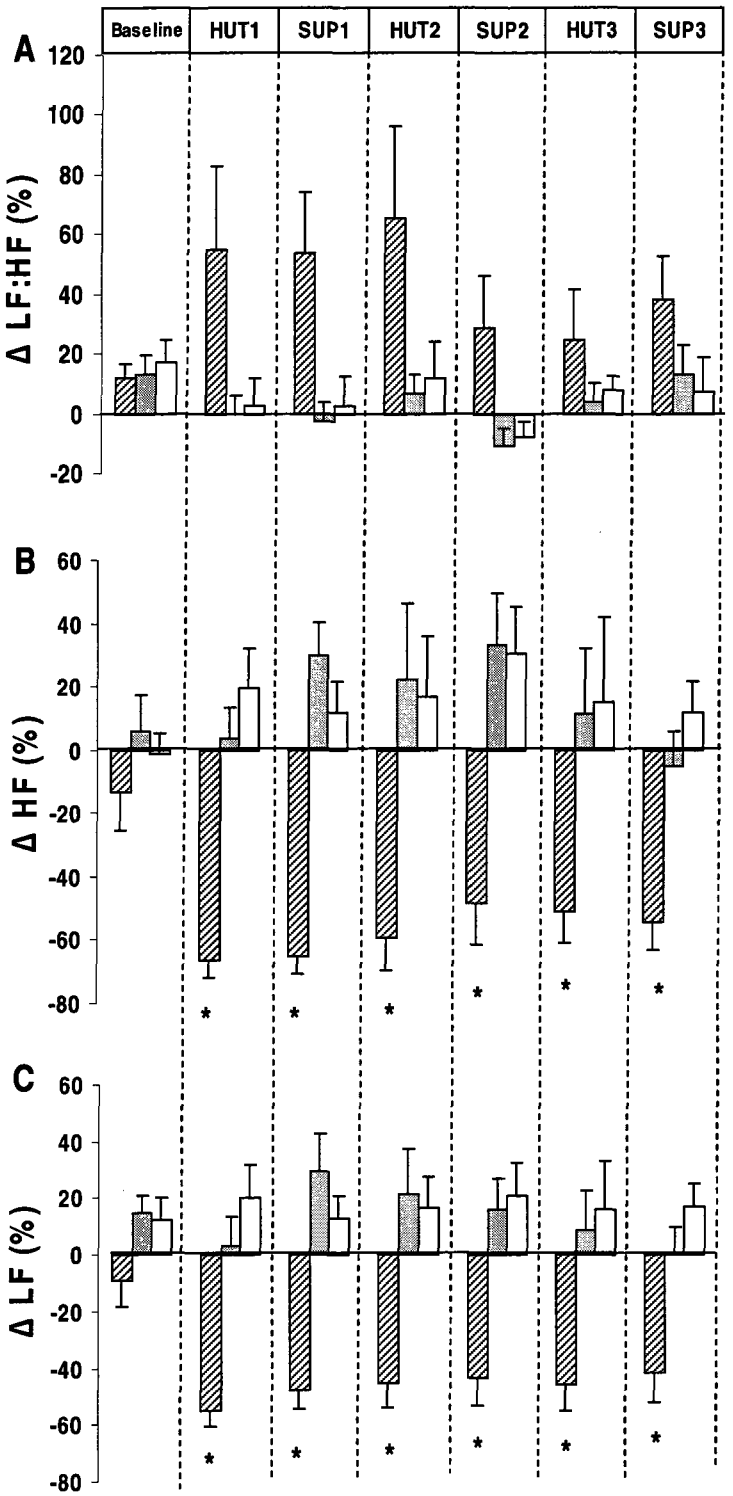

Figure 3. Relative % change in frequency-domain measures of HRV (△LF:HF power, panel A), (△HF power, panel B), and (△LF power, panel C) from the non-heat stress control trial as measured during repeated 70° head-up tilts performed in the early (stripped bars) and late stages [24-hr (grey bars) and 48-h (white bars)] of recovery following exercise-induced hyperthermia. Values are means ± SE. Significant differences between non-heat stress control and post-exercise hyperthermia are denoted by an asterisk (*), $p<0.05$.

PART THREE:

GENERAL CONCLUSIONS OF THE THESIS

The primary purpose of the first article was to evaluate the short-term postexercise cardiovascular and thermoregulatory responses to repeated orthostatic challenges performed following exercise-induced hyperthermia (rectal temperature ≥39.5°C). It is evident from our findings that despite substantial postexercise hypotension and reductions in baroreceptor sensitivity elicited through exercise performed in the heat, the cardiovascular system is able to preserve mean arterial pressure and cardiac output during repeated 70° head-up tilts. Despite higher levels of thermal strain, sustained reductions in cutaneous vascular conductance were observed with each successive head-up tilt which suggests a nonthermal baroreceptor mediated modulation of cutaneous vascular conductance. In contrast, a nonthermal baroreceptor mediated attenuation of local sweat rate was not observed which may indicate that local sweat rate is unaffected by baroreflex mediated influences under a state of elevated hyperthermia. The important finding that postural stress alters thermoregulatory control during higher levels of hyperthermia should be taken into consideration for military (pilots) and civilian (firefighters) personnel, industrial workers (miners), astronauts, and athletes who may encounter orthostatic challenges under conditions of elevated thermal strain. Efforts should be made to reduce postural or orthostatic stress following a hyperthermic episode especially in the early stages of recovery. Individuals should be encouraged to recover in a supine or head-down tilt position until mean arterial pressure has been re-established to near baseline resting levels.

The objective of the second article was to determine if severe hyperthermia induced through exercise in the heat can alter autonomic nervous system function in the short-term recovery period and if so, to evaluate the long-term residual consequences of altered ANS function during repeated orthostatic challenges presented 24 and 48-h postexercise. It is clear from our findings that severe hyperthermia, causes a short-term reduction of both BRS and HRV which is exacerbated by postural stress. However, measures of BRS and HRV were restored by 24-h of recovery following exercise-induced hyperthermia. The novel observation of orthostatic hypertension (i.e., greater ΔMAP) following 24-h of recovery demonstrates the importance of evaluating the impact of hyperthermic exercise on long-term blood pressure control. While the elevation in arterial blood pressure cannot be explained by changes in BRS and/or HRV, it is plausible that the exercise-induced hyperthermia resulted in changes in fluid balance due to dehydration and an acute loss of plasma volume causing a time-dependent increase in blood pressure. Our findings provide important information regarding ANS function following exercise-induced hyperthermia in young healthy males. However, it is well known that ANS function is compromised with aging and chronic disease (Ferrari, 2002; Goldberger *et al.*, 2002) and therefore the response of the system during combined orthostatic and heat-stress in vulnerable populations warrants further investigation.

PART FOUR:

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PART FIVE:

APPENDIX

Health Sciences and Science REB ethical clearance certificate

Université d'Ottawa University of Ottawa

HEALTH SCIENCES AND SCIENCE RESEARCH ETHICS BOARD

CERTIFICATE OF ETHICAL APPROVAL

This is to certify that the University of Ottawa Health Sciences and Science Research Ethics Board has examined the application for ethical approval of the research project entitled **Autonomic Nervous System Function after Exercise-induced Hyperthermia (H 05-08-05)** submitted by Pr. Glen Kenny of the School of Human Kinetics at the University of Ottawa and Miss Rachel Armstrong.
The Board found that this research project met appropriate ethical standards as outlined in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards, and accordingly gave it a Category 1a (approval). This certification is valid one year from the date indicated below.

June 17, 2008
Date

Germain Zongo
Protocol Officer for Ethics in Research
For Dr. Daniel Lagarec, Chair of the
Health Sciences and Science REB