POST-EXERCISE RESPONSES DURING TREATMENT DELAYS DO NOT AFFECT THE PHYSIOLOGICAL RESPONSES TO COOLING IN COLD WATER IN HYPERTHERMIC INDIVIDUALS

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ABSTRACT

Victims of exertional heat stroke (EHS) in whom treatment is delayed have higher rates of multi-organ failure and a greater number of fatalities. Death related to EHS is preventable, through immediate treatment via cold-water immersion (CWI). To date little is known about the influence of treatment delays on core cooling following EHS. Thus we sought to examine the effects of treatment delays on cardiovascular and thermal responses prior to, during, and following CWI treatment in individuals with exercise-induced hyperthermia.

Our findings demonstrate that treatment delays resulted in a sustained level of hyperthermia and cardiovascular strain that significantly increased the time an individual is at risk to the potential lethal effects of EHS. Moreover, we report that cold water immersion treatment is powerful enough to overcome the adverse effects of treatment delays and rapidly reduce core temperatures while facilitating the re-establishment of blood pressure towards normal resting levels.

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PART ONE: EMPIRICAL AND THEORETICAL CONSIDERATIONS

CHAPTER 1

INTRODUCTION

1.0 Introduction

Exercise or physical exertion in hot, humid environments while a necessary component of many occupations including professional athletes, firefighters, miners and military members (Rav-Acha et al. 2004, Roberts 2005, Armstrong et al. 2007) can severely compromise an individual's ability to dissipate heat to the environment resulting in a thermal imbalance (Cheung et al. 2000). A thermal imbalance between the rate of heat production and the rate of total heat loss to the surrounding environment directly results in body heat storage (S) and significant increases in core temperature (T_{co}) (Webb 1995, Kenny et al. 2008). When an individual's T_{co} approaches 40°C the risk of sustaining exertional heat stroke (EHS) is greatly elevated. EHS is defined as a rectal temperature (T_{re}) > 40°C (Bouchama and Knochel 2002, Armstrong et al. 2007) and is characterized by central nervous system disturbances and multiple organ system failure, and can be denoted by confusion, disorientation, dizziness, irrational behaviour, irritability headache, profound fatigue, hyperventilation, vomiting and diarrhea (Armstrong et al. 2007). Lack of immediate recognition and accurate temperature assessment combined with ineffective or delayed treatment can result in fatalities from EHS (Heled et al. 2004, Roberts 2005, Armstrong et al. 2007).

The maintenance of internal body temperature independent of the ambient environmental temperature (T_a) is critical for survival. Regulation of body temperature would appear to be achieved primarily by thermal factors through vasomotor tone responding to the prevailing ambient temperature, void of any changes in metabolic heat

production or evaporative heat loss. However, independent of thermal control, nonthermal factors such as exercise, post-exercise, hydration state, sleep etc., influence responses of the thermoregulatory system (Mekjavic and Eiken 2006, Kenny and Journeay 2010). Increases in metabolic heat production such as physical exertion or exercise and/or exposure to a warmer T_a elicit a thermoregulatory response including elevations in skin blood flow and sweating in order to facilitate an increased rate of heat loss. These responses are moderated by a hypothalamic feedback loop that integrates afferent sensory inputs with appropriate efferent thermal responses (Boulant 2006, Mekjavic and Eiken 2006). Under certain circumstances such as environmental conditions of high T_a and/or relative humidity (RH) combined with sustained physical exertion the thermal responses are not sufficient to maintain heat balance resulting in body heat storage (Cheung et al. 2000). Furthermore exercise and thermoregulation impose competing demands on the cardiovascular system, with exercise requiring large amounts of blood flow for muscular work, and thermoregulatory responses (to exercise and/or heat stress) require increases in skin blood flow concurrently, subjecting the cardiovascular system to a significant physiological strain (Rowell 1974).

At the cessation of exercise the thermal responses must continue to remove the accumulated stored body heat to reduce the individual's T_{co} to pre-exercise levels (Journeay et al. 2006). However current literature demonstrates that local skin blood flow and sweating post-exercise are markedly reduced during the early stages of recovery despite residual body heat storage (Journeay et al. 2004, Journeay et al. 2006, Kenny et al. 2006, Kenny et al. 2007, Kenny and Journeay 2010). It is believed that the post-exercise thermal responses are not due to a hypothalamic shift of set-point temperature but are a result of non-thermal factors that determine post-exercise cardiovascular status such as central command,

mechanoreceptors and baroreceptors (Journeay et al. 2006, Kenny and Journeay 2010). Post-exercise hemodynamic responses are separated into early stage (responses are influenced by subsequent changes in input from central command, mechanoreceptor and metaboreceptor feedback), and late stage (post-exercise hypotension) (Journeay et al. 2006). A study by Gagnon et al examining the influence of nonthermal factors on post-exercise heat loss in hyperthermic (end-exercise esophageal temperature of 39.5ºC) individuals showed that the thermal drive in the hyperthermic conditions dominated nonthermal factors in the regulation of CVC early in recovery, and has an overriding influence over sweat rate until the later stages of recovery (Gagnon et al. 2008).

Recovery from dynamic exercise has been shown to result in a compromised thermoregulatory control as evidenced by a prolonged elevation in T_{co} (Thoden et al. 1994). The post-exercise elevations in core temperature are influenced by the convective heat transfer from previously active musculature to the core combined with post-exercise hypotension (Kenny et al. 2006). It has been suggested that the elevations in core temperature would persist in the absence of a post-exercise increase in heat loss response, as long as the heat content of the muscle remains greater than the core and hypotension persists (Kenny et al. 2002, Kenny et al. 2003). Thus the rate of core temperature decay is therefore limited to changes in surface heat loss through evaporative and non-evaporative mechanisms (Kenny et al. 2003).

Effective treatment for EHS requires immediate whole body cooling via a cooling modality that has sufficient cooling rates to reduce T_{co} to near normal baseline resting levels within 30 min (Roberts 2005, Casa et al. 2006, Armstrong et al. 2007, Casa et al. 2007, Casa and Kenny 2010). Cold water immersion (CWI) has been shown to have some of the highest

cooling rates in the current literature (Costrini 1990, Armstrong et al. 1996, Proulx et al. 2003, Casa et al. 2007, Mazerolle et al. 2010). A study by Proulx et al (Proulx et al. 2003) comparing cooling rates for a large range of water temperatures (2°C - 20°C) demonstrated that 2°C ice water produced a cooling rate approximately twice that of warmer water, based on measurements of rectal temperature (T_{re}). Recently Taylor et al (Taylor et al. 2008) demonstrated that temperate water immersion reduced esophageal temperature (T_{es}) to 37.5°C in less than 3 min (or a cooling rate comparable to that measured during CWI) and concluded that effective heat loss can be achieved without CWI. However, it must be noted that T_{es} can be reduced to 37.5°C while T_{re} remains greater than 39°C indicating significant residual heat storage likely remains in the visceral organs with the possibility of further thermal damage (Casa and Kenny 2010).

The ACSM position statement on Exertional Heat Illness (EHI) during training and competition recommends that immediate recognition of EHS followed by immediate treatment by whole body cooling is paramount for survival (Armstrong et al. 2007). Furthermore the National Athletic Trainers' Association Position Statement: Exertional Heat Illness, recommended to; 1) measure T_{re} to determine (recognize) if an athlete is suffering from EHS, 2) assess cognitive function, 3) lower T_{co} as fast as possible by immersing the body in an ice water bath (Binkley et al. 2002). Therefore it is apparent that individuals suffering from EHS require early recognition and immediate effective treatment in order to enhance chances of survival without any residual effects (O'Donnell and Clowes 1972, Costrini 1990, Roberts 2005, Casa et al. 2007). Furthermore current research has shown that T_{re} is the only reliable and valid measurement of deep tissue temperature to accurately assess the T_{co} of an individual in the field that has been exerting themselves in the heat (Binkley et

al. 2002, Casa et al. 2007, Ronneberg et al. 2008, Ganio et al. 2009). However despite current education of athletic trainers in North America a study by Mazerolle et al., demonstrated that less than one-fifth of athletic trainers surveyed used rectal thermometers to assess T_{co}, and only one half used cold water immersion to treat EHS (Mazerolle et al. 2010). This inaccurate temperature assessment leads to a misdiagnosis of the severity of the hyperthermia of the individual which can lead to a delay and /or lack of treatment or use of an inefficient cooling modality. Further exacerbating this problem can be a delay in the time taken to activate Emergency Medical Services (EMS) paralleled by the response time of EMS personnel. The total pre-hospital time to care (delay in treatment) of EMS personnel includes the response interval defined as the time of activation to arrival on-scene, the on-scene time which includes time from arrival to reaching the patient and recovering the patient to the ambulance, and lastly the departure time from the scene to arrival at the hospital (Carr et al. 2006, Silverman et al. 2007). From the period of August 1st 2009, to July 31st 2010 Ottawa paramedics responded to 104 heat stress related calls with an average on scene time of ~8 min, scene time of ~19 min and transport to hospital time of ~14 min for a total pre-hospital time to care of ~41 min respectively (unpublished data). Other studies have shown similar response times for EMS personnel (Carr et al. 2006, Silverman et al. 2007). Moreover, this information assumes immediate treatment for the EHS victims when they arrive at the hospital which may not always be the case.

1.1 Rationale

Current guidelines clearly state the need for immediate recognition and treatment for individuals suffering from EHS (Binkley et al. 2002, Armstrong et al. 2007). And research has shown a high survival rate with little if any residual complications if individuals are

accurately diagnosed early and treated immediately with an effective cooling modality that reduces T_{co} to < 40°C within 30 min (O'Donnell and Clowes 1972, Costrini 1990, Roberts 2005, Casa et al. 2007). However despite current knowledge of EHS recognition, prevention and treatment there has been significant rise in hospitalizations and deaths from EHS in the US Army between 1980 and 2002 (Carter et al. 2005). The National Center for Catastrophic Sport Injury Research has shown that the highest number of fatalities due to EHS in American sport occurred from 2005-2009 (Research 2010). Therefore EHS continues to be problematic for military members involved in training and operations as well as athletes training and competing in the heat. Furthermore work by Mazerolle et al., demonstrate that although the majority of athletic trainers are aware of the current guidelines for treating EHS they are not following "best practices" of T_{re} assessment and CWI, leading to misdiagnosis and delays or lack of treatment (Mazerolle et al. 2010). The reasons cited for not using CWI included: a lack of resources, field location (i.e. no access to water supply, facility not conducive to that treatment modality), success using other methods, potential cardiovascular shock and other safety issues (i.e. drowning, vasoconstriction, syncope) (Mazerolle et al. 2010). Moreover whole body immersion resources and facilities are not always readily available and thus the EHS victim must then rely on EMS (O'Hara et al. 2008, Mazerolle et al. 2010). A number of factors can contribute to the total pre-hospital time to care including inaccurate temperature assessment resulting in delays in activation of EMS, response times of EMS personnel, the increased number of EMS calls during a heat emergency (Dolney and Sheridan 2006), and other higher priority calls happening concurrently (Silverman et al. 2007). Lastly, current research investigating the post-exercise cardiovascular and thermal responses removes all subjects from the heat stress condition to a cooler and/or thermoneutral environment during recovery and hence initiating recovery immediately. No

studies to date have examined the effects of a delay in treatment time on cardiovascular and thermal responses of hyperthermic individuals (T_{re} of 40°C) whereby heat loss has been compromised during post-exercise recovery. The combined effects of a prolonged thermal and cardiovascular strain on subsequent cold water immersion have not been studied thus leaving a dearth of information in this area.

1.2 Statement of the Problem

Physical exertion is a component of many different occupations such as firefighting, mining and military operations. Often times, individuals are required to work in the heat exposing them to increases in core temperature termed exercise induced hyperthermia, which can lead to exertional heat illness, emergency medical situations and even death (Carter et al. 2005). The post-exercise thermal and cardiovascular responses to individuals with exercise induced hyperthermia (EIH) are a topic of current investigation however the majority of studies completed begin treatment or remove participants to a thermoneutral environment immediately. Despite our current understanding of the cardiovascular responses that occur following exercise-induced hyperthermia, little is known about the consequences of altered cardiovascular function on the efficacy of CWI treatment. Whether or not the alterations in cardiovascular function are exacerbated by delays in treatment and thereby affect the efficacy of the cooling treatment (i.e. CWI) of the hyperthermic victim remains unclear.

1.3 Objectives

The primary objective of this study is to investigate the effects of delays in treatment on the cardiovascular and thermal responses prior to, during and following ice-water immersion in EIH individuals. The aim of the current study was to create a model that simulated the cardiovascular instability (i.e. severe hypotension) with a compromised ability

to dissipate heat experienced by an EHS victim in whom treatment is delayed (O'Donnell and Clowes 1972, Costrini et al. 1979). Thus, post-exercise recovery following intense exercise in the heat will be conducted in an upright seated posture under a significant heat load to simulate dry heat gain from the environment while restricting evaporative heat loss. The information gained from the completion of this research project will provide insight on the physiological responses to EHS for health professionals and influence the decision as weather to immediately treat EHS victims or transport them to a hospital first.

1.4 Hypothesis

We tested the hypothesis that delays in treatment for an individual with EIH will result in a sustained elevation of core temperature paralleled by a progressively greater hypotension accompanying further increases in the duration of the treatment delay. We believed that this hyperemia coupled with blood pooling would trap heat in the previously active musculature. We also tested the hypothesis that this reduction of heat transfer from the muscle to the core and core to the periphery would result in an attenuated core cooling rate and greater immersion times during subsequent treatment via ice-water immersion. Furthermore, the greater immersion times associated with treatment delay would result in a greater after drop and longer subsequent recovery times.

1.5 Relevance

This study will give us a better understanding of the consequences of a delay in treatment on the thermal and cardiovascular responses prior to, during and following treatment of EIH victims using ice-water immersion as a treatment modality. Furthermore the results of this study will add to the existing body of evidence of post-exercise thermoregulatory responses.

Treatment modalities for EIH are not always be readily accessible in the field therefore individuals do not always receive treatment in a timely manner. Thus information regarding the effects on physiologic responses (thermal and cardiovascular) due to delays in treatment time may help in setting field treatment protocols.

1.6 Limitations

The main limitation of the study is the inability to evaluate the effect of the treatment delay on an individual with EHS. Relative humidity can reach full saturation (100%) in ambient environmental conditions however the percentage of relativity humidity for this study will be set at 20% in order to ensure that no damage is inflected to our measurement equipment. Only male subjects were used for this study and thus comparisons between sexes cannot be made. Females were excluded from the study as they have been shown to have different responses with respect to post-exercise blood pressure regulation following exercise in the heat compared to endurance trained males (the population recruited for this study). The effects of physical characteristics (i.e. lean body mass, body mass to surface area, body stature etc.) will not be controlled for this study.

1.7 Delimitations

The study requires that participants are physically active and are able to tolerate exercise in the heat until their T_{re} reaches 40°C. Although participants will be classified as severely hyperthermic, the results of the study will not apply to individuals whose T_{re} reach levels > 40°C. Furthermore participants for the study will be mainly recruited from the University of Ottawa campus and will generally be aged between 18 and 35 years, thus the results will not apply to children, the elderly or to a sedentary or unfit population. Lastly, although the study will be the first to examine the effects of delays in treatment time in

hyperthermic individuals the mode of attaining hyperthermia will be via exercise and therefore comparisons to individuals suffering from classic heat stroke will not be valid.

CHAPTER 2

REVIEW OF LITERATURE

2.0 Thermoregulation

The purpose of body heat regulation is to maintain body heat balance independent of the ambient environmental conditions (Webb 1995). Thermoregulation is the integrative process of regulating T_{co} within narrow limits through the adjustment of physiological mechanisms in order to obtain a balance between the heat produced by the body and the heat lost to the environment (Kenny and Journeay 2010). Internal body temperature including the visceral organs and tissues is regulated within a narrow band near 37°C, where as skin temperature is generally cooler than internal temperature and varies throughout the body.

Physiological regulation of core body temperature is achieved through graded control of heat production and heat loss responses through a complex system requiring numerous physiological mechanisms to maintain thermal balance. The autonomic nervous system integrates thermal information from the core and skin. The preoptic area and anterior hypothalamus (PO/AH) is identified as a thermosensitive region (Boulant 2006) that receives afferent temperature information from warm sensitive and cold sensitive neurons in the spinal cord and thermoreceptors located in the skin (Hensel 1973). Temperature changes sensed by the PO/AH result in appropriate effector heat production or heat loss responses based on the magnitude of the thermal disturbance. That is minor disturbances are regulated through vasomotor tone controlling cutaneous vasodilation and vasoconstriction, where as major perturbations induce the more powerful responses of sweating or shivering respectively (Webb 1995, Mekjavic and Eiken 2006).

2.0.1 Heat Exchange

In order to maintain heat balance the human body must be able to exchange heat with the surrounding environment. Convection, radiation and evaporation are the dominant means of heat exchange with the environment. Convection is the transfer of heat through the movement of a medium such as gas or liquid from a high concentration to a lower one, such as the gradient between the body core and the periphery. When air moves over the skin surface the warm air close to the skin is replaced by cooler air improving the gradient, thus enhancing the heat loss between the skin and the environment. Convection also serves to transfer heat within the body through the blood by perfusion of warm blood with cooler tissues. Heat exchange with the environment through electromagnetic waves is known as radiation, those specific to heat balance are mainly infrared (Brooks 2005). Evaporation is the transfer of heat from the evaporation of sweat from the surface of the skin and is the most powerful means of heat dissipation during exercise in a hot and dry ambient environment. The amount of heat removed from the skin surface is essentially 2426 KJ/kg at 30°C, equal to the heat of vaporization (Wenger 1972). Lastly conduction is the transfer of heat through direct contact of two surfaces, and is generally negligible in a sporting or occupational environment.

2.1.2 Thermoregulatory Responses during Exercise

Heat stress caused from a hot humid environment can elicit heat loss responses, however sustained physical exercise ordinarily accounts for the greatest physiological strain on the thermoregulatory system. Metabolic heat production during exercise can increase by 10-20 times with less than 30% of the energy liberated is converted to mechanical energy. Therefore more than 70% of the metabolic heat generated by exercise must be transported to

the skin to be dissipated to the environment. Body heat storage and increases in core body temperature occur when the rate of heat production is greater than the rate of total heat dissipation to the surrounding environment (Gisolfi and Wenger 1984). When the body begins to store heat the convective heat transfer between muscle and blood causes a continued increase in body heat storage and thus body core temperature. Exercise intensity, environmental conditions and an individual's physiological characteristics all influence the rate and magnitude of heat storage (Kenny et al. 1997). Furthermore in the absence of heat loss core body temperature can increase ~ 1°C every 5 min and thus the individual would be in danger of heat illness within 15 min (Gisolfi and Wenger 1984, Armstrong et al. 2007).

The heat dissipating responses to increases in core body temperature include increases in sudomotor activity (activation of the sweating response), increases in skin blood flow and peripheral vasodilation (Gisolfi and Wenger 1984). In the absence of sweating, increases in skin blood flow carrying heat from the core to the skin, increase skin temperature and promote heat loss from the skin to the environment. In the presence of sweating the increase in skin blood flow provides the heat required to evaporate the sweat from the skin surface (Gisolfi and Wenger 1984). Dilation of the superficial veins further promotes heat loss by increasing the time available and the surface area for conductive heat exchange between the blood and the skin. The onset of exercise elicits immediate heat production due to the release of energy required for mechanical work however the heat loss response is much slower resulting in increased heat storage and core body temperature until heat dissipation matches heat production.

2.1.3 Cardiovascular Responses to Heat Stress

One of the main pathways humans use to dissipate heat involves convective heat transfer from the core to the skin via skin blood flow. Heat exposure or passive heat stress occurs when the surrounding environmental conditions are such that skin temperature is elevated severely limiting conductive heat dissipation, and placing the cardiovascular system under pronounced physiological strain. Generally the skin receives ~ 500 mL or 5-10% of cardiac output in thermoneutral environments, however under heat stress through either heat exposure or exercise skin blood flow can increase up to 8 liters per minute or ~50-70% of cardiac output (Kenney and Johnson 1992, Charkoudian 2003). During passive heat stress the primary cardiovascular challenge to thermoregulation results from impairment of venous return that is as skin blood flow increases blood pools in the large dilated cutaneous vascular bed thus, reducing central blood volume and impairing cardiac filling (Rowell 1974). Therefore to prevent large decreases in arterial blood pressure cardiac output must increase, primarily mediated by increases in heart rate, along with decreases in vascular conductance of non-cutaneous beds (Rowell 1983, Crandall and Gonzalez-Alonso 2010).

The body's main control mechanism for blood pressure is the baroreceptor reflex pathway. That is, when mean arterial pressure (MAP) decreases the baroreceptors are unloaded triggering an increase in sympathetic activity resulting in an increase in heart rate, myocardial contractility and vasoconstriction. In contrast loading of the baroreceptors results in an increase in parasympathetic activity resulting in a decrease in heart rate and vasomotor tone. Current evidence does not demonstrate that baroreceptor control of heart rate to significant changes in arterial blood pressure is negatively influenced by passive heat stress (Crandall and Gonzalez-Alonso 2010).

Central blood volume decreases as a result of heat exposure, which is likely due to a redistribution of blood volume from the core to the cutaneous vascular beds coupled with increases in cardiac output. In a study by Crandall et al., looking at the effects of passive heating on central blood volume the authors observed typical hemodynamic responses including a reduction in central venous pressure accompanied by reductions in thoracic blood volume, heart blood volume and the central vascular structures (Crandall et al. 2008).

2.1.4 Cardiovascular Responses to Exercise and Heat Stress

It is widely accepted that the cardiovascular system responds to the metabolic requirements of exercise by increasing cardiac output via increases in heart rate (HR) and stroke volume (SV). This is primarily achieved due to parasympathetic withdrawal and sympathetic stimulation of the heart and redistribution of blood flow from splanchnic and renal tissues to cutaneous and working muscle tissue through sympathetic modulation of vascular resistance. Therefore during exercise the cardiovascular system is placed under considerable physiological strain as the thermoregulatory response of increased skin blood flow (SkBF) directly competes with the demand for blood flow by the working muscle. This phenomenon is partially mediated by a redistribution of blood flow from the renal and splanchnic regions to the working muscle (Rowell 1974, Charkoudian 2003). However progressive declines in SV, central venous pressure (CVP), mean arterial pressure (MAP), and central blood volume coupled with increases in HR to maintain cardiac output are key indicators of cardiovascular strain during exercise and heat stress (Rowell 1983, Crandall and Gonzalez-Alonso 2010). When SkBF and active muscle are in competition for cardiac output thermoregulatory demands do not lead to a diversion of blood flow from active muscle (Gonzalez-Alonso et al. 2008) thus compromising the body's ability to dissipate heat

resulting in increases in T_{co} and body heat storage thereby increasing the risk of thermal injury.

2.1.5 Hydration Exercise and Heat Stress

The strain placed on the cardiovascular system when heat stress is combined with exercise due to the competition between the thermoregulatory and cardiovascular systems for blood flow is augmented when dehydration is present. Gonzalez-Alonso et al., demonstrated a decrease in venous pressure and total peripheral resistance which in turn led to a decrease in ventricular filling and stroke volume along with a corresponding compensatory increase in heart rate to maintain cardiac output and blood pressure in individuals rendered hyperthermic by exercise in the heat (Gonzalez-Alonso et al. 1997). A 7-8% decrease in stroke volume coupled with an increased heart rate sufficient to prevent a significant decline in cardiac output was found in individuals that were either euhydrated and hyperthermic or dehydrated and normothermic (Gonzalez-Alonso et al. 1997). However, the combination of hyperthermia and dehydration during exercise in the heat resulted in a greater decline in stroke volume (20%) and a synergistic decline in cardiac output (13%) (Gonzalez-Alonso et al. 1997). This indicates that the strain experienced by the cardiovascular system during exercise in the heat is exacerbated when sweat loss is not replaced and dehydration occurs.

2.2 Post-exercise Thermoregulation

Physical exertion particularly during dynamic exercise requires muscular work that leads to metabolic heat production resulting in body heat storage and increases in T_{co}. At the cessation of exercise this residual heat stored in the body must also be dissipated to the environment via the thermoregulatory mechanisms of SkBF and sweating. However, numerous studies have shown a prolonged elevation in T_{co} persisting for durations greater

than 60 min post-exercise, indicating a compromised thermoregulatory response following dynamic exercise (Thoden et al. 1994, Kenny and Niedre 2002, Kenny et al. 2006). Furthermore despite elevations in core body temperature studies have also shown a rapid decrease in sudomotor activity and local skin blood flow to pre-exercise levels during the early stages of recovery (Kenny and Niedre 2002, Journeay et al. 2004, Gagnon et al. 2008).

Recovery from dynamic exercise results in significant adjustments of the cardiovascular system. Based on the previously described relationship between the cardiovascular system and heat dissipation it is plausible that the factors influencing post-exercise cardiovascular recovery may also influence post-exercise thermal responses and subsequently core body temperature regulation (Kenny et al. 2007, Kenny et al. 2010). Under thermoneutral conditions moderate intensity dynamic exercise for 30-60 min will elicit a post-exercise hypotensive response (Kenney and Seals 1993). That is, with the cessation of exercise cardiac output declines rapidly while the systemic vascular resistance takes longer to recover to pre-exercise levels resulting in post-exercise hypotension (PEH) observed as a decrease in MAP (Halliwill 2001). The magnitude and duration of this decrease in MAP is influenced by the intensity of the completed exercise (Kenny and Niedre 2002, Kenny et al. 2006). The PEH is typically characterized by a reduction in venomotor tone resulting in a drop in systemic vascular resistance that is not offset by cardiac output (Halliwill 2001). Therefore the increased venous compliance resulting in an increased cutaneous venous volume coupled with the withdrawal of the musculoskeletal pump and reduction in HR following the termination of exercise results in a reduction in MAP post-exercise (Halliwill 2001, Gagnon et al. 2008). Furthermore the removal of the musculoskeletal pump coupled with an upright seated posture promotes venous and muscle blood pooling thus inhibiting

cardiac filling and unloading cardiopulmonary baroreceptors (Piepoli et al. 1993, Halliwill 2001). Possible mechanisms attributed to the sustained decrease in vasomotor tone are a resetting of the baroreflex to maintain a lower blood pressure following exercise thus reducing sympathetic vasomotor outflow combined with an impaired vascular response to sympathetic outflow (Halliwill et al. 1996, Halliwill et al. 2003).

Studies have shown that post-exercise SkBF and local sweat rate are also influenced by non-thermal factors such as central command and mechanoreceptors / muscle pump (Journeay et al. 2004, Kenny et al. 2010). However further evidence suggests that PEH associated with the baroreceptor modulation of SkBF and local sudomotor activity is the paramount non-thermal influence responsible for the post-exercise thermoregulatory response (Journeay et al. 2004, Journeay et al. 2004, Kenny et al. 2006, Kenny et al. 2010). This hypothesis is supported by studies demonstrating that the post-exercise attenuation of SkBF and sweat rate is reversed by reducing the post-exercise unloading effect on the baroreflex in the early stages of recovery through the application of positive pressure to the lower limbs, head-down tilt and supine recovery (Journeay et al. 2004, McInnis et al. 2006, Kenny et al. 2008). Thus the aforementioned perturbations in post-exercise thermoregulatory control may be attributed to a non-thermal baroreceptor input coupled with a post-exercise hypotensive response (Kenny and Journeay 2010).(Ducharme and Tikuisis 1994, Kenny et al. 2003)

2.3 Treatment for EHS

The risk of EHS is ever present for any soldier, athlete, laborer, or other individual who undertakes physical exertion or exercise in hot or warm ambient environment, resulting in a potentially lethal outcome (Binkley et al. 2002, Carter et al. 2005, Armstrong et al. 2007,

Casa et al. 2007). Current guidelines on exertional heat illness state that immediate recognition of EHS followed by immediate treatment via whole body cooling is paramount for survival (Binkley et al. 2002, Heled et al. 2004, Armstrong et al. 2007). Furthermore effective treatment for EHS requires a cooling modality with sufficient rectal temperature cooling rates to reduce T_{re} by 0.1-0.2°C/min when cooling begins immediately or by greater than 0.15°C/min when treatment is delayed beyond 30 min (Armstrong et al. 2007). A review by Casa et al, comparing the effectiveness of various cooling modalities by comparing their associated cooling rates determined that cold water and ice water immersion (2°C) displayed superior cooling rates and that the powerful cooling capacity provided by CWI offers the best chance of survival for EHS victims (Casa et al. 2007). This conclusion is supported within the literature with studies showing that the highest cooling rates are achieved with the use of CWI (Costrini 1990, Armstrong et al. 1996, Proulx et al. 2003, McDermott et al. 2009, Mazerolle et al. 2010). A study by Proulx et al, compared cooling rates during whole body immersion for a wide range of temperatures (2°C – 20°C), demonstrated that the highest rates of cooling based on T_{re} were achieved through 2°C ice water (0.35°C/min) almost two times greater than that of warmer water (Proulx et al. 2003). Furthermore studies have shown a 100% survival rate for EHS victims that are treated immediately with CWI or within a few minutes after collapse or presentation of symptoms (O'Donnell and Clowes 1972, Costrini 1990, Casa and Kenny 2010).

Despite the substantial evidence demonstrating the efficacy of CWI as the most effective treatment for EHS some individuals argue that rapid and effective heat loss can still be achieved using temperate water immersion (Taylor et al. 2008, Casa and Kenny 2010). They argue that T_{es} provides a superior approximation of blood temperature travelling to the

central nervous structures and that T_{re} while adequate during slow temperature changes is inadequate during dynamic phases (Casa and Kenny 2010). Taylor et al recently demonstrated that whole body immersion in temperate water (26°C) reduced T_{es} to 37.5°C in less than 3 min and despite lower cooling rates concluded that effective treatment for EHS can be achieved with temperate water (Taylor et al. 2008). Furthermore they contend that CWI elicits cutaneous vasoconstriction that impedes CVC and therefore convective heat delivery to the periphery is reduced compared to temperature water immersion and that sudden cold immersion can result in significant and adverse physiological changes (cold shock response) (Taylor et al. 2008, Casa and Kenny 2010). However, the thermoregulatory response to hyperthermia is dictated by the hypothalamus and the temperature it perceives from the core (Casa et al. 2007) where as the influence of skin temperature is secondary to core temperature. Reductions in core temperature have a slower temporal response, which effectively blunts the normal physiological responses to immersion in cold water in hyperthermic individuals.

Total body heat loss provides a more objective evaluation of cooling modalities than core body temperature response (Casa and Kenny 2010). Heat gained through dynamic exercise may not be completely dissipated through the short immersion time required to restore T_{es} to 37.5°C resulting in significant residual body heat storage likely remaining in the visceral organs, with a corresponding $T_{re} \geq 39$°C with the possibility of further thermal damage (Casa and Kenny 2010). Moreover, Proulx et al demonstrated that heat dissipation through conduction / convection is not impeded despite the induction of cutaneous vasoconstriction attributed to ice water immersion (Proulx et al. 2006), and the impressive

survival rate of EHS victims treated with ice water baths demonstrated above outweighs any possible adverse physiological effects from CWI.

2.3.1 Factors influencing EHS Treatment

Individuals suffering from EHS have a high survival rate with little if any residual complications if they are accurately diagnosed early and treated immediately with an effective cooling modality that reduces T_{co} to less than 40°C within 30 minutes (O'Donnell and Clowes 1972, Costrini 1990, Roberts 2005, Casa et al. 2007). Unfortunately many athletes and soldiers today who sustain EHS still have fatal outcomes. Therefore despite the advancements in the knowledge of EHS recognition, prevention and treatment this has not translated to current practice in the field as seen by a significant rise in hospitalizations for EHS in the US Army between 1980 and 2002 and recent data regarding EHS fatalities in organized American sport (Carter et al. 2005, Research 2010). A current study by Mazerolle et al., that surveyed 498 high school and college athletic trainers as identified through the National Athletic Trainer's Association (NATA), found that although the athletic trainers have sound knowledge regarding the correct means for recognition (rectal temperature) and treatment (ice water immersion) only a limited number (18.6%) used rectal thermometers to assess core body temperature and the majority (50.3%) used means other than ice water immersion to treat EHS victims (Mazerolle et al. 2010). The diagnosis of EHS is characterized by severe hyperthermia (T_{co} >40°C) and CNS dysfunction (Binkley et al. 2002, Armstrong et al. 2007). To accurately assess the core body temperature of an individual that has been performing physical activity in the heat the measurement must be a valid predictor of deep body temperature uninfluenced by external factors such as sweat, fluid intake, clothing etc, to ensure a clear picture of the degree of acute hyperthermia. The literature

clearly demonstrates that axillary, tympanic, temporal, oral and skin measurements are not valid or reliable predictors of deep body temperatures, thus medical staff should rely solely on rectal temperature assessment to determine the severity of hyperthermia (Binkley et al. 2002, Casa et al. 2007, Ronneberg et al. 2008, Ganio et al. 2009).

Notwithstanding accurate assessment and recognition of EHS, individuals can still succumb to the thermal damage induced from severe hyperthermia if effective treatment is not rapidly initiated. The critical element determining the outcome from EHS is not the peak core body temperature attained but rather the amount of time that the individual remains above 40°C (Roberts 2005). It is critical that core body temperature of an EHS victim is reduced to less than 40°C within 30 min after collapse (Costrini 1990, Casa et al. 2007, McDermott et al. 2009). Therefore a treatment modality must be immediately accessible and must cool the deep body tissue rapidly enough for T_{co} to be reduced sufficiently to meet the above criteria in order to be effective. CWI as previously described is the gold standard for rapid cooling however whole body immersion facilities may not always be readily accessible (O'Hara et al. 2008, Mazerolle et al. 2010).

2.4 Delays in Treatment Time

It has been clearly demonstrated that it is imperative for individuals that are suffering from EHS immediately undergo an accurate assessment and that effective treatment commences promptly post diagnosis. Furthermore to ensure the precise severity of hyperthermia the initial core body temperature measurement must be taken via rectal temperature. A study by Casa et al., comparing the validity of various temperature measurement devices on individuals exercising in the heat found that temperature assessed at oral, axillary, aural and temporal sites were not valid and tended to under-predict core body

temperature values (Casa et al. 2007). Therefore body temperature measurements taken at these sites through various devices may lead to a misdiagnosis as to the severity of the hyperthermia and as such a delay or lack of treatment and/or use of an inefficient cooling modality. Moreover, an under-predicted core body temperature value may provide a false sense of security in regards to the severity of the hyperthermia leading to a delay in the activation of Emergency Medical Services (EMS). Response times of EMS personnel are another factor that can cause considerable delays in time to treatment for individuals suffering from EHS. An initial look at response interval times reveals an average time of ~5.22 min (Carr et al. 2006) for EMS personnel however, further investigation uncovers that response interval time only accounts for the time at which the call was received (alarm) until the ambulance arrives on scene (arrival) (Carr et al. 2006, Silverman et al. 2007). The total pre-hospital time to care (delay in treatment) includes not only response intervals but also on-scene time interval defined as time from arrival on-scene to departure, and transport to hospital interval defined as time from scene departure to arrival at the hospital, assuming immediate care upon arrival at the hospital. A meta-analysis by Carr et al investigating total pre-hospital time to care for trauma patients over a 30 year period, analyzed 155, 179 patients and determined the average total delay in treatment time to be 30.96 min for urban, 30.97 min for suburban, 43.17 min for rural areas respectively (Carr et al. 2006). Furthermore information obtained from the Ottawa Paramedic Service (unpublished data) for response times for 104 calls from hyperthermic patients during the period encompassing August 1st 2009, to July 31st 2010 displayed an average response interval of ~8 min, an average on-scene interval of ~19 min, and an average transport time of ~14 min for a total average pre-hospital time to care of ~41 min respectively. Casa et al. has also reported a delay of at least 45 min when waiting for an ambulance to arrive (Casa et al. 2012). Other

factors that can affect the response times from EMS personnel responding to calls from hyperthermic individuals include an increased number of calls during heat emergencies (Dolney and Sheridan 2006) and call priority with highest priority calls such as cardiac arrest being attended to first (Silverman et al. 2007).

It is clear that early recognition and immediate treatment for individuals suffering from EHS significantly improve chances of survival with little to no residual effects. However a number of factors can contribute to delays in time to treatment for EHS victims including inaccurate temperature assessment, response times of EMS personnel, increased number of EHS victims during heat emergencies and higher priority calls occurring simultaneously. Furthermore there have been no studies to date investigating the cardiovascular and thermal responses to delays in treatment time. Additionally, all of the current literature examining the cardiovascular and thermal responses during recovery from dynamic exercise in the heat, all subjects are moved to a thermoneutral or cooler environment leaving a significant gap in this area of research.

PART TWO: METHODS & RESULTS

CHAPTER 3

METHODOLOGY

3.0 Participants

Eight healthy (no history of respiratory, metabolic or cardiovascular disease) men aged between 18 and 45 years, participated in the study. It should be noted that two volunteers who were recruited for the study could not increase their T_{re} to 40ºC and were thus excluded from participating in the study. Participants were recruited from the University of Ottawa campus and the National Capital Region. Participants were physically active at least three times a week for a minimum of 20 minutes at a medium to hard intensity (12 or more on the Borg Scale,) (Borg 1982). Participants currently on medication or with any history of medication or heart problems and/or blood pressure irregularities were excluded from the study. All volunteers were required to complete one familiarization session and three experimental trials conducted on different days with a minimum of 48 hours separation between trials. All trials were performed at the same time of day for each participant to control for circadian variation in skin and core temperatures (Webb 1995). All testing sessions were performed at the Human and Environmental Physiology Research Unit (HEPRU), School of Human Kinetics, in the environmental chamber located on the 3rd floor of Montpetit Hall (MNT 309,310 and 311), University of Ottawa campus.

3.1 Preliminary Instructions

Each participant was instructed to refrain from alcohol and the use of non-steroidal anti-inflammatory drugs for 48 hours, severe or prolonged physical activity for 24 hours, caffeine for 12 hours and to refrain from eating or smoking for at least two hours, prior to each laboratory session. In addition, participants were asked to refrain from other thermal

stimuli, such as exercise, sauna, and/or hot tub immersion the day of experimental trials in order to avoid confounding effects of increased metabolic rates and core temperature.

3.2 Familiarization session

Individuals completed one familiarization session that was approximately one hour in duration. During this session participants were introduced to all the measurement techniques and instrumentation that were used during the experimental sessions. Participants signed an informed consent form (Appendix A) and completed a Physical Activity Readiness Questionnaire (Par-Q) as well as the American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire (AHA screening) (Balady et al. 1998).

3.2.1 Anthropometrics

Once informed consent was obtained basic anthropometric measurements, including height, mass, and body composition, were taken.

Height

Participants positioned themselves in front of the standard Detecto scale (Detecto, Webb City, MO, USA), stood erect, with their arms by the sides, feet together, and heels and back were in contact with the wall. They were instructed to look straight ahead, stand as tall as possible, and take a deep breath while the measurement was taken. The set square was lowered on top the head depressing the hair to make firm contact and the measurement was taken at the level of the lower border of the set square on the measuring rod. The distance from the floor to the lower border of the set square was recorded to the nearest 0.5 cm.

Body Mass

A calibrated digital high capacity Mettler Toledo IND560 scale (Mettler Toledo Canada, Mississauga, ON) was used to measure the participants body mass. The scale was placed on the floor and the subjects (nude) were instructed to step onto the scale. The participants body mass were recorded to the nearest 0. 1 kg.

Body Composition

Lean body mass (LBM), and percent body fatness, was calculated via hydrostatic weighing from the measurement of body density and employment of the Siri equation (Siri 1956) to estimate percent body fatness. Participants entered the hydrostatic weighing tank wearing only their bathing suit, and were instructed to remove all air bubbles from clothing and hair, and sit in the chair harness. After a few breaths of quiet breathing, participants were instructed to expel all of the air from their lungs and sit quietly, completely submerged under water for five seconds for data collection. Measurements were collected by custom LabVIEW software. In order to obtain accurate results the procedure was repeated five times and the average of the five measurements were used.

3.2.2 Maximal Exercise Test ($VO_{2\ peak}$)

A Graded Exercise Test (GXT) was conducted to determine participants' maximal aerobic capacity (VO_{2max}) and maximum HR which was used to set the workloads for the experimental sessions. Expired gases were collected using the MOXUS (AEI Technologies Inc., Naperville, IL, USA) automated metabolic measurement system. Prior to the commencement of the test, each participant warmed-up for five minutes during which time the speed that was utilized throughout the duration of the test was determined (in consultation with the participant). Subsequently, the specific protocol for each subject (including speed and elevation progression) was verbally explained. Participants were fitted

with a Hans Rudolph two-way non-rebreathing valve (Hans Rudolph Inc, Kansas, USA) mouthpiece, nose clip and head support, as well as a Polar Wear Link coded transmitter (Model FS1, Polar Electro Canada Inc, Lachine, QC) to monitor heart rate. The first two minutes of the treadmill test consisted of running at an initial grade of 0%. Thereafter, the treadmill incline was increased by 2% every 2 minutes until volitional fatigue, at which time the test was terminated. The subject was notified that they could have stopped the test at any time without prejudice. Criteria for the termination of the VO_{2max} test included:

- onset of angina (chest pain) or angina-like symptoms;
- signs of poor perfusion – light headedness, confusion, pallor (pale appearance to the skin), cyanosis (bluish discoloration);
- ataxia (failure of muscular coordination), nausea, or cold and clammy skin;
- participant requested to stop;
- volitional fatigue;
- physical or verbal manifestations of severe fatigue;
- failure of testing equipment;
- shortness of breath, wheezing, leg cramps, and/or
- failure of HR to increase with increased exercise intensity (Thompson 2010).

3.3 Experimental Protocols

Upon arrival to the laboratory participants inserted a rectal temperature probe, voided their bladder and weighed themselves nude. Subsequently they donned shorts, socks and running shoes and sat quietly at an ambient temperature (23°C) while being instrumented. Participants were required to sit quietly for ~75 min prior to testing for all of the measurement devices to be attached and verified. Once all the equipment and probes (see below) were in place and functioning, baseline data was collected for twenty minutes, including thermal (T_{re}, T_{es}), cardiovascular (HR, cardiac output (CO)) and hemodynamic (BP). Following baseline data collection participants were then moved into a thermal chamber (40°C, 20% relative humidity (R.H.)) where they remained seated in an upright

seated posture for an additional twenty minute seated resting period. Following the rest period participants donned a nylon poncho (to limit evaporative heat loss) for the exercise period. Participants ran continuously on a treadmill at exercise intensity of 65% of VO_{2max}, (~40 min) as determined by the familiarization session, until reaching a T_{re} of 40°C at which time the test was terminated. Participants needed to reach a T_{re} of 40°C in order to be included in the data analyses. Participants were informed that they could terminate the test at any time without prejudice, and criteria for the termination of the test are listed above (Thompson 2010). For every 0.5°C increase in T_{re} T_{es}, HR, and Real Time were documented. Furthermore, HR, T_{re}, and T_{es}, were documented every five min during the duration of the test.

Upon reaching a T_{re} of 40°C, participants removed the nylon poncho and returned to an upright seated resting position in the thermal chamber (40°C, 20% RH) and donned a nylon sleeveless running jacket. The nylon jacket was worn to simulate and environment with a greater RH where evaporative heat loss would be limited. Participants remained resting in the thermal chamber for the duration of the pre-trial randomized treatment delay. The treatment delays consisted of either a short (5 min), moderate (20 min), or prolonged (40 min) duration. Participants were informed at the beginning of each trial as to what the treatment delay time would be for the respective trial.

Following the pre-determined treatment delay, participants were moved to a circulating ice water bath (Hayward Whirlpool, City of Industry, CA, USA) within the thermal chamber (40°C, 20% RH) maintained at 2°C for treatment by CWI. To minimize cold water discomfort, participants donned neoprene socks and were immersed to the nipples in a recumbent position. Participants remained in the ice water bath until T_{re} was reduced to 37.5°C to ensure that the heat gained during exercise was eliminated without any possible

residual effects from hyperthermia. Water temperature was controlled by monitoring temperature with a digital thermocouple and adding ice as needed. Re-warming techniques consisted of drying the participant and covering them in warm blankets and a jacket was used following CWI treatment.

Upon reaching the exit T_{re} of 37.5°C, participants exited the ice bath during which time the physiological variables were monitored for an additional minimum of 30 min, or until T_{re} returned to ~36.5°C. Participants took a second measure of nude body mass following the conclusion of the trial.

3.4 Instrumentation

Rectal temperature was measured continuously using a pediatric thermocouple probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical, St-Louis, MO, USA) inserted into the rectum, 10-12 cm past the anal sphincter. All instrumentation has been previously described (Kenny and Niedre 2002, Kenny et al. 2008, Wright et al. 2010).

Esophageal temperature was measured continuously by placing a pediatric thermocouple probe of approximately 2 mm inch diameter (Mon-a-therm Nasopharyngeal Temperature Probe, Mallinckrodt Medical, St-Louis, MO, USA) through the participant's nostril while they sipped water through a straw. The location of the probe tip in the esophagus was estimated to be in the region bounded by the left ventricle and aorta, corresponding to the level of the eighth and ninth thoracic vertebrae, and determined using a regression equation to approximate the level of the heart (Mekjavic and Rempel 1990): Insertion Length (cm) = 0.228 x (standing height) – 0.194.

Skin temperature was measured continuously at 9 points over the body surface using 0.3 mm diameter T-type (copper/constantan) thermocouples integrated into heat-flow sensors

(Concept Engineering, Old Saybrook, CT, USA). Thermocouples were attached using surgical tape (Blenderm, 3M, St. Paul, MN, USA). The calculation to determine area-weighted mean skin temperature was based on the regional proportions reported by Hardy & Dubois (Hardy and Dubois 1937) and was modified from what has been previously described by Proulx et al. (Proulx et al. 2003). During the immersion period the head, chest, upper back and upper arm were not entirely immersed in the cold water bath thus they were not used to calculate mean skin temperature and rates of non-evaporative heat loss using the regional proportions of Hardy & Dubois (Hardy and Dubois 1937).

Heart rate was monitored continuously using a Polar coded transmitter, recorded continuously and stored with a Polar VantageTM interface and Polar Precision Performance software (Model FS1, Polar Electro Oy, Finland). Blood pressure was monitored before and after the exercise period. Blood pressure was measured through auscultation of the brachial artery using a mercury sphygmomanometer every five minutes during baseline, resting and the treatment delay periods. It was measured more frequently (i.e., every two minutes) during the CWI treatment period. Mean arterial pressure (MAP) was calculated using the formula: ⅓ systolic pressure + ⅔ diastolic pressure. Oxygen consumption was measured using a metabolic cart (MOXUS Modular Metabolic System) during the maximal capacity assessment. During the experimental trials, an Oxycon Mobile (Viasys HealthCare Inc., Hoechberg, Germany) was used to monitor breath-by-breath oxygen consumption during the resting data collection and immersion phases of the trials.

Cardiac Output was measured using a non-invasive inert gas re-breathing technique (Innocor^{TM}, DK-5260 Innovisions, Odense, Denmark) that has been previously validated against the direct oxygen Fick method and thermodilution (Peyton and Thompson 2004). With their nose plugged, participants breathed through a mouthpiece into the closed re-

breathing system, comprised of a 3-way respiratory valve connected to an antistatic rubber bag and an infrared photoacoustic gas analyzer. The time points at which measurements of CO were taken were as follows: 1) end of the 20 min baseline resting period in thermoneutral conditions, 2) at the end of the 20 min pre-exercise rest period in the heat, 3) at 5-min post-exercise (note: this was the only measurement point for the 5-min delay period), 4) at the end of the treatment delay period (i.e., at 5, 20 and 40-min post-exercise for the short, moderate and prolonged exercise recovery conditions), and 5) at the end of post-immersion recovery. Values for total peripheral resistance (TPR) and stroke volume (SV) were calculated as: TPR = MAP/CO; and SV = CO/HR, respectfully.

Measurements of nude body weight were obtained prior to and following each experimental session using a digital high-performance scale (IND560, Mettler Toledo Canada, Mississauga ON). Results were recorded to the nearest 0.1 kg. Venous blood was collected via an indwelling intravenous catheter (BD Insyte™ Autoguard™, 18G, BD, Franklin Lakes, NJ) in a superficial vein. Approximately 5 mL was drawn into a sterile plastic syringe and transferred immediately into plasma K_2EDTA 5.4 mg BD Vacutainer® tubes (BD, Franklin Lakes, NJ) for immediate hematologic analyses. Blood samples were drawn at the following time points: 1) end of the 20 min baseline resting period in thermoneutral conditions; 2) at the end of the 20 min pre-exercise rest period in the heat; 3) at 5-min post-exercise (note: this was the only measurement point for the 5-min delay period); 4) at the end of the treatment delay period (i.e. at 5-, 20- and 40-min post-exercise for the short, moderate and prolonged exercise recovery conditions); and 5) at the end of post-immersion recovery. Hematocrit and haemoglobin concentrations were analyzed in duplicate and determined using the Coulter method (Coulter® A^c•T diff 2^{TM} analyzer,

Beckman Coulter, Miami, FL, USA). Changes in plasma and blood volumes from baseline levels were estimated from changes in hemoglobin and hematocrit using the formula proposed by Dill et al. (Dill and Costill 1974). Values are reported as means for duplicate measures respectively.

3.5 Data Analysis

The core temperature values for baseline resting (i.e. thermoneutral ambient conditions) were averaged over the final 5 min. The rates for whole-body heating [change in (Δ) temperature/exercise time], and core cooling during CWI (Δ temperature/immersion time) were calculated for both T_{re} and T_{es} measures. The core cooling rates were calculated from pre-immersion temperature ($T_{pre\text{-}imm}$) (i.e. the core temperature value immediately prior to the start of immersion) values for both T_{re} and T_{es} measures. They were assessed by 1) examining the overall cooling rates as calculated by the time it took for each core temperature measure to reach 37.5°C and 2) the rate of cooling measured for the 1st degree Celsius reduction in temperature ($T_{pre\text{-}imm}$ - 1°C) and 2nd degree Celsius reduction in temperature [($T_{pre\text{-}imm}$ - 1°C) - 1°C) for each condition respectively. The break point or delay (lag) period in minutes at which T_{re} cooling started to decrease following the start of immersion was determined by segmental linear regression analysis using Graph Pad Prism software v5.0 (GraphPad Software Inc., La Jolla, CA, USA). The core temperature nadir (the lowest core temperature measured following CWI), the time to reach core temperature nadir and the time to recovery were also determined. Core cooling rates were compared between conditions based on overall time to reach a rectal temperature of 37.5°C. The first and second degree Celsius reductions in core temperature were also compared between conditions.

3.6 Statistical Analysis

A common time point relative to all conditions (i.e. 5-min post-exercise) was used to make comparisons. Comparisons were made between baseline resting values (i.e. rest in the thermoneutral ambient temperature), 5-min post-exercise, end of treatment delay and end of post-immersion recovery (i.e. when T_{re} returned to 36.5°C) for all experimental conditions. A two way repeated measures analysis of variance (ANOVA) with the repeated factors of time (5-min post-exercise; end of treatment delay) and condition (short; moderate; and prolonged) was used to analyze the effects of treatment delays on the dependent variables [thermal (T_{re}, T_{es}, and MT_{sk}); cardiovascular (CO, MAP, TPR, HR and SV); as well as blood and plasma volume]. In separate analyses we determined the effects of treatment delay relative to baseline resting values as well as end of post immersion recovery in each group using repeated measures ANOVA. A two-way repeated measures ANOVA was used to analyze $H_{sk,}$ MT_{sk} and rates of metabolic heat production during every minute of the immersion period with the repeated factor of time (0, 1, 2, 3, 4, 5, 6, 7, 8, 9 min etc. to the last common immersion point) and the repeatable factors of experimental condition (short, moderate and prolonged). Comparisons for heating and cooling rates, time to cool, time to reach core temperature nadir, time to end recovery and changes in body mass between experimental conditions were performed utilizing a one-way repeated measure ANOVA. When a significant main effect was observed *post hoc* comparisons were conducted using paired samples *t*-tests. All analyses were performed using the statistical software package SPSS 20 for Windows (SPSS Inc. Chicago, IL, USA) and the level of significance was set at $p \leq 0.05$. The alpha level was adjusted during multiple comparisons to maintain the rate of type I error at 0.05 using the Bonferroni ($P \leq 0.05/N$; N = number of comparisons) correction.

Cooling rate is not affected by Treatment Delays in Hyperthermic Individuals

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Abstract

Death related to exertional heat stroke is preventable through the immediate treatment via cold water immersion (CWI). To date little is known about the influence of treatment delays on cardiovascular and thermal responses prior to, during, and following CWI treatment in individuals with exercise-induced hyperthermia. We compared the effects of either a short (5-min), moderate (20-min), or prolonged (40-min) treatment delay on subsequent CWI in eight males rendered hyperthermic [rectal temperature (T_{re}) of 40°C] through exercise in the heat. We measured thermal [esophageal temperature (T_{es}), T_{re}] and cardiovascular (cardiac output, heart rate and blood pressure) variables as well as plasma and blood volumes. Core temperature was significantly elevated above baseline (short T_{re}:36.91±0.10; T_{es}:36.82±0.10; moderate T_{re}:36.86±0.07; T_{es}:36.88±0.05; and prolonged T_{re}:36.84±0.09; T_{es}:36.72±0.10°C) at 5-min post-exercise (T_{re}:40.08±0.06; T_{es}:39.79± 0.10°C) and remained elevated throughout the moderate (T_{re}:39.96±0.10; T_{es}:39.33±0.20°C) and prolonged (T_{re}:39.61±0.09; T_{es}:38.58±0.14°C) delays. Mean arterial pressure was markedly reduced at 5-min post-exercise (75±2.6 mm Hg) relative to baseline values (92±1.8 mm Hg) and remained reduced prior to immersion (moderate:74±1.7 mm Hg; and prolonged:70±2.1 mm Hg). Core cooling rates (short T_{re}:0.20±0.01; T_{es}:0.47±0.03; moderate T_{re}:0.17±0.02; T_{es}:0.45±0.01; and prolonged T_{re}:0.17±0.01; T_{es}:0.41±0.03ºC/min) were similar between conditions. We show that core cooling rates were unaffected by the delay in treatment which resulted in a pronounced and sustained state of hyperthermia paralleled by marked deterioration in cardiovascular function. We conclude that CWI remains a safe and effective treatment modality for exertional hyperthermia when treatment is delayed up to 40 min.

Key words: Cold Water Immersion, Cardiovascular Strain, Heat Stress, Exercise Recovery

Introduction

Strenuous physical activity performed in hot ambient conditions can often exceed the body's physiological capacity to dissipate heat, resulting in dangerous increases in core temperature. The situation can be exacerbated by conditions whereby a sufficiently high rate of heat loss cannot be attained or maintained (i.e. intense exercise in hot/humid conditions, clothing insulation, dehydration, etc.). The most serious heat related illness is exertional heat stroke (EHS), a condition marked by an elevated core body temperature (> 40.0–41.0°C), failing sweating mechanisms (Coris et al. 2004), and central nervous system (CNS) dysfunction (Armstrong et al. 2007, O'Connor et al. 2010). Victims of EHS typically demonstrate a precipitous drop in blood pressure which is exacerbated by the exercise-induced state of hypovolemia (Costrini et al. 1979). The main criterion determining the survival of individuals with EHS is the length of time that core temperature remains above critical values (Hubbard et al. 1977).

Studies show that the body's ability to dissipate heat following dynamic exercise is attenuated as evidenced by a marked reduction of whole-body heat loss leading to a sustained elevation in core and muscle tissue temperatures. This impairment in thermoregulatory capacity can persist for as long as 2 hours post-exercise (Kenny and Journeay 2010). The disturbance in post-exercise thermoregulation is paralleled by a pronounced drop in arterial blood pressure which can persist for at least 90 minutes following dynamic exercise. The impairment in both thermoregulatory and cardiovascular function is exacerbated with increases in the level of heat stress associated with a greater rate of metabolic heat production (exercise intensity) and/or environmental (air temperature, solar radiation, etc.) heat load (Kenny and Journeay 2010, Halliwill et al. 2013). In the case of an

EHS victim, if left untreated for a prolonged period, such a compromised ability to dissipate heat combined with an already elevated state of hyperthermia can result in confusion, delirium, coma, convulsions, liver dysfunction, increased intestinal permeability (leading to endotoxemia) and other complications (Stearns 2011). In parallel, the loss of underlying cardiovascular compensatory responses can lead to circulatory collapse/syncope (O'Donnell and Clowes 1972, Costrini et al. 1979, Zeller et al. 2011) placing the EHS victim at even greater risk of suffering from a myriad of organ dysfunctions and in some cases death if not promptly cooled (Stearns 2011).

Early recognition and immediate on-site treatment of EHS optimizes the survival rate of EHS victims. Cold water immersion (CWI) is recognized as the gold standard treatment for EHS (Armstrong et al. 2007, Casa et al. 2007, Casa and Kenny 2010), as it has produced some of the highest recorded core temperature cooling rates (Costrini 1990, Armstrong et al. 1996, Proulx et al. 2003, Casa et al. 2007). However, much of our knowledge pertaining to the effectiveness of CWI in the treatment of exercise-induced hyperthermia is derived from studies in which the immersion in cold water occurred immediately (within 5 min) upon cessation of exercise. As such, it is unclear if the effectiveness and safety of this treatment modality may be negatively impacted by the deterioration in physiological function typically observed in EHS victims who are left untreated and remain exposed to conditions which may further compromise their already tenuous state of health (i.e. remain exposed to hot/humid conditions, clothed, dehydrated, etc.) for extended periods. These delays in treatment can result from an inaccurate diagnosis or recognition of the condition (Casa et al. 2007, Casa et al. 2012), the time required for transport to treatment facilities (~20 min), as well as a considerable wait for first responders (~40 min) (Carr et al. 2006, Marom et al. 2011, Casa et

al. 2012). Regardless of the underlying reasons, treatment delays can result in multi-organ failure, longer hospitalizations and a greater number of fatalities (Zeller et al. 2011).

The aim of the current study was to examine the effect of treatment delays of 5-, 20- and 40-min duration on the efficacy of CWI in the treatment of individuals rendered hyperthermic [rectal temperature (T_{re}) of 40.0°C] during prolonged treadmill running in the heat (ambient air temperature of 40.0°C). In order to simulate an elevated state of cardiovascular (i.e. marked hypotension) and thermal (i.e. elevated state of hyperthermia and attenuated rate of heat loss) strain typically observed in EHS victims left untreated for prolonged periods, participants recovered in the upright seated posture while in a hot environment (40.0°C). A sleeveless running jacket covering the torso was used to restrict whole-body heat loss during post-exercise recovery. We evaluated the hypothesis that delays in treatment time would result in a sustained elevation of core temperature exacerbated by greater hypotension with longer durations of delays in treatment. This would be paralleled by a decrease in core cooling rate during subsequent CWI. The greater immersion times associated with treatment delays would result in a greater core temperature after-drop and longer subsequent recovery times following CWI treatment.

Materials and methods

The experimental protocol for this study was approved by the University of Ottawa Health Sciences and Science Research Ethics Board in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to their participation in the study.

Participants

Eight healthy (non-smoking, free of any known cardiovascular, respiratory or metabolic diseases) physically active (exercised minimum of 30 min, 3-5 times/week) males participated in the study. Their physical characteristics were as follows (mean ± SD): age, 30 ± 6 years; height, 180 ± 6 cm; weight, 79.6 ± 9.1 kg; maximum oxygen consumption, 59.8 ± 4.2 $mLO_2 \cdot kg^{-1} \cdot min^{-1}$; percentage of body fat, 13.4 ± 3.0 %; and body surface area, 1.99 ± 0.14 m^2.

Experimental Protocol

All participants completed one preliminary and three experimental sessions separated by a minimum of 48 hrs. During the preliminary session informed consent was obtained followed by measurements of participants' nude body mass, height, body density, and maximum oxygen consumption. Nude body mass was measured using a calibrated digital high capacity scale (IND560, Mettler Toledo Canada, Mississauga ON) while body height was determined using a stadiometer (model 2391; Detecto, Webb City, MO, USA). Body density was measured by hydrostatic weighing and used to calculate lean body mass and percent body fat with the Siri equation (Siri 1956). Maximum oxygen consumption was measured by indirect calorimetry (MOXUS system, Applied Electrochemistry, Pittsburgh, PA, USA) during a graded exercise test performed on a treadmill (Woodway Desmo, Woodway USA, INC., Waukesha, WI, SA) in thermoneutral conditions [22ºC, 39% Relative Humidity (RH)]. Participants were instructed to refrain from alcohol and the use of non-steroidal anti-inflammatory drugs for 48 hours, severe or prolonged exercise for 24 hours, and caffeine for 12 hours as well as food consumption for 2 hours prior to each session.

Water consumption was not restricted prior to or during the conduct of each session. Experimental sessions were conducted at the same time of day for each participant to avoid circadian variations in core temperature.

Upon arrival at the laboratory, participants voided their bladder, inserted a temperature probe in their rectum and weighed themselves nude. Subsequently, they donned standardized athletic clothing (i.e. shorts, t-shirt and running shoes) and sat quietly outside the temperature controlled chamber at an ambient temperature (23°C) while being instrumented. Following instrumentation, they remained resting for 20 min in order to measure normal resting values. Participants then moved into a thermal chamber maintained at 40°C and 20% RH and remained seated for an additional 20 min during which time pre-exercise resting values were recorded. Participants subsequently donned a nylon poncho and ran continuously on a treadmill at ~65% of their maximal oxygen consumption, until T_{re} reached 40.0°C. Thereafter, the nylon poncho was removed, and replaced with a light sleeveless nylon running jacket. The participant was then required to sit in an upright seated resting position for either a short (5-min), moderate (20-min) or prolonged (40-min) post-exercise recovery period to simulate treatment delay in the temperature controlled chamber at 40°C (20% RH). Note: for the purposes of this presentation, this post-exercise recovery period will be referred to as the treatment delay period. Following the treatment delay, participants donned neoprene socks and entered a circulated ice water bath (2°C) located in the temperature controlled chamber (Hayward Whirlpool, City of Industry, CA, USA). They were immersed to the nipples while in an upright seated position with both arms out of the bath until T_{re} was reduced to 37.5°C. Upon reaching a T_{re} of 37.5ºC they exited the cold water bath, and sat upright in the thermal chamber (40ºC, 20% RH) until T_{re} returned to near baseline resting values (i.e. ~36.5°C) (minimum of 20 min).

Measurements

Esophageal (T_{es}) and T_{re} were measured with general purpose thermocouple temperature probes (Mallinckrodt Medical Inc., St-Louis, MO, USA). The T_{es} probe was inserted 40 cm past the entrance of the nostril while the participants sipped water (250-500 mL) through a straw. The T_{re} probe was inserted to a depth of 15 cm past the anal sphincter. Skin temperature and non-evaporative heat loss (H_{sk}) were measured at 9 sites using T-type (copper/constantan) thermocouples integrated into heat flow sensors (Concept Engineering, Old Saybrook, CT, USA). The area-weighted mean skin temperature (MT_{sk}) and H_{sk} were calculated using the following regional proportions: forehead 9.4%, upper back 11.75%, lower back 11.75%, abdomen 11.75%, quadriceps 12.75%, hamstring 12.75%, calf 8.72%, bicep 9.39% and chest 11.75%. During the immersion period the head, chest, upper back and upper arm were not entirely immersed in the cold water bath thus, the percentages for the MT_{sk} during immersion are calculated as follows: lower back 20.1%, abdomen 20.1%, quadriceps 22.35%, hamstring 22.35%, and calf 15.1%. Temperature and heat flow data were collected using a HP Agilent data acquisition module (model 3497A) at a rate of one sample every 15 s and simultaneously displayed and recorded in spreadsheet format on a personal computer with LabVIEW software (Version 7.0, National Instruments, TX, USA).

Cardiac Output (CO) was measured using a non-invasive inert gas (0.5% nitrous oxide and 0.1% sulfur hexafluoride) re-breathing technique (Innocor^{TM}, DK-5260 Innovisions, Odense, Denmark) that has been previously validated against the direct oxygen Fick method and thermodilution (Peyton and Thompson 2004). With their nose plugged, participants breathed through a mouthpiece into the closed re-breathing system, comprised of a 3-way respiratory valve connected to an antistatic rubber bag and an infrared photo

acoustic gas analyzer. The time points at which measurements of CO were taken were as follows: 1) end of the 20 min baseline resting period in thermoneutral conditions; 2) at the end of the 20 min pre-exercise rest period in the heat; 3) at 5-min post-exercise (note: this was the only measurement point for the short delay period); 4) at the end of the treatment delay period (i.e. at 20- and 40-min post-exercise for the moderate and prolonged exercise recovery conditions); and 5) at the end of post-immersion recovery. Values for total peripheral resistance (TPR) and stroke volume (SV) were calculated as: TPR = MAP/CO; and SV = CO/HR, respectfully.

Heart rate (HR) was monitored continuously using a Polar coded transmitter combined with a Polar heart rate monitor (Model FS1, Polar Electro Oy, Kempele, Finland), and measurement samples were documented every 5 min during the trial. Blood pressure (BP) was measured by auscultation of the brachial artery every 5 min during the baseline resting periods in thermoneutral and hot ambient conditions as well as during the treatment delay periods. Measurements were performed every 2 min during the CWI period. Mean arterial pressure (MAP) was calculated using the formula: ⅓ systolic pressure + ⅔ diastolic pressure. Oxygen consumption was measured on a breath by breath basis and averaged over 15 s using a portable metabolic measurement system (Oxycon Mobile, Viasys HealthCare Inc., Hoechberg, Germany) during the resting and immersion periods only.

Measurements of nude body weight were obtained prior to and following each experimental session using a digital high-performance scale (IND560, Mettler Toledo Canada, Mississauga ON). Results were recorded to the nearest 0.1 kg. Venous blood was collected via an indwelling intravenous catheter (BD Insyte™ Autoguard™, 18G, BD, Franklin Lakes, NJ) in a superficial vein. Approximately 5 mL was drawn into a sterile

plastic syringe and transferred immediately into plasma K_2EDTA 5.4 mg BD Vacutainer® tubes (BD, Franklin Lakes, NJ) for immediate hematologic analyses. Blood samples were drawn at the end of each time period prior to transition (i.e. baseline, rest, 5-min post-exercise, end of treatment delay and end of recovery) similar to CO as noted above. Hematocrit and haemoglobin concentrations were analyzed in duplicate and determined using the Coulter method (Coulter® A^c•T diff 2^{TM} analyzer, Beckman Coulter, Miami, FL, USA). Changes in plasma volume (PV) and blood volume (BV) from baseline levels were estimated from changes in haemoglobin and hematocrit using the formula proposed by Dill and Costill (1974). Values are reported as means for duplicate measures.

Data Analysis

Both T_{re} and T_{es} values for the baseline resting (i.e. thermoneutral ambient conditions) period was averaged over the final 5 min. The rates for whole-body heating [change in (Δ) temperature/exercise time], and core cooling during CWI (Δ temperature/immersion time) were calculated for both T_{re} and T_{es} respectively. The core cooling rates were calculated from pre-immersion temperature ($T_{pre\text{-}imm}$) (i.e. the core temperature value immediately prior to the start of immersion) values for both T_{re} and T_{es} measures. They were assessed by 1) examining the overall cooling rates as calculated by the time it took for each core temperature measure to reach 37.5°C and 2) the rate of cooling measured for the 1st degree Celsius reduction in temperature ($T_{pre\text{-}imm}$ - 1°C) and 2nd degree Celsius reduction in temperature [($T_{pre\text{-}imm}$ - 1°C) - 1°C) for each condition respectively. The break point or delay (lag) period in minutes at which T_{re} cooling started to decrease following the start of immersion was determined by segmental linear regression analysis using Graph Pad Prism software v5.0 (GraphPad Software Inc., La Jolla, CA, USA). The

lowest T_{re} and T_{es} value (nadir) measured following CWI, the time to reach the nadir for both T_{re} and T_{es} as well as the time to recovery (T_{re} of ~36.5°C) were also determined.

Statistical Analysis

A common time point relative to all conditions (i.e. 5-min post-exercise) was used to make comparisons. Comparisons were made between baseline resting values (i.e. rest in the thermoneutral ambient temperature), 5-min post-exercise, end of treatment delay and end of post-immersion recovery (i.e. when T_{re} returned to 36.5°C) for all experimental conditions. A two way repeated measures analysis of variance (ANOVA) with the repeated factors of time (5-min post-exercise; end of treatment delay) and condition (short; moderate; and prolonged) was used to analyze the effects of treatment delays on the dependent variables [thermal (T_{re}, T_{es}, and MT_{sk}); cardiovascular (CO, MAP, TPR, HR and SV); as well as blood and plasma volumes]. In separate analyses we determined the effects of treatment delay relative to baseline resting values as well as end of post immersion recovery in each group using repeated measures ANOVA. A two-way repeated measures ANOVA was used to analyze $H_{sk,}$ MT_{sk} and rates of metabolic heat production during every minute of the immersion period with the repeated factor of time (0, 1, 2, 3, 4, 5, 6, 7, 8, 9 min etc. to the last common immersion point) and the repeatable factors of experimental condition (short, moderate and prolonged). Comparisons for heating and cooling rates, time to cool, time to reach core temperature nadir, time to end recovery and changes in body mass between experimental conditions were performed utilizing a one-way repeated measure ANOVA. When a significant main effect was observed *post hoc* comparisons were conducted using paired samples *t*-tests. All analyses were performed using the statistical software package SPSS 20 for Windows (SPSS Inc. Chicago, IL, USA) and the level of significance was set at $p \leq 0.05$.

The alpha level was adjusted during multiple comparisons to maintain the rate of type I error at 0.05 using the Bonferroni ($P \leq 0.05/N$; N = number of comparisons) correction.

Results

There were no differences in baseline resting values for thermal (T_{re}, T_{es}, and T_{sk}) and cardiovascular (CO, HR, SV, MAP and TPR) variables (all $p > 0.05$; Table 1).

Exercise Period

Exercise time taken to reach the experimental criterion end-point (i.e. T_{re} of 40.0°C) was similar between conditions (short: 37.8 ±10.7 min; moderate: 41.4 ± 5.0 min; and prolonged: 42.8 ±13.7 min) (p=0.602). In parallel, end-exercise T_{re} and T_{es} were similar between conditions (Figure 1). As such the core heating rates during exercise were not different for T_{re} (short: 0.09 ± 0.02ºC/min; moderate: 0.08 ± 0.01 ºC/min; and prolonged: 0.08 ± 0.02 ºC/min; p=0.418) or T_{es} (short: 0.09 ± 0.02 ºC/min; moderate: 0.09 ± 0.01 ºC/min; and prolonged: 0.08 ± 0.03 ºC/min; p=0.378) respectively. There were no differences in rates of metabolic heat production between conditions prior to exercise (short: 123 ± 9 W; moderate: 123 ± 11 W; and prolonged: 120 ± 11 W; p = 0.753).

Delay of treatment Period

Both T_{re} and T_{es} remained significantly elevated from baseline values at 5-min post-exercise and the end of treatment delay for all conditions ($p < 0.000$; Figure 1). No differences between conditions were measured in thermal responses at 5-min post-exercise (all $p > 0.05$; Table 1). Whereas a significant reduction in T_{es} was measured for both the moderate and prolonged conditions at end of treatment delay relative to 5-min post-exercise, T_{re} differed only for the prolonged condition (all $p < 0.05$).

While CO and HR were significantly elevated from baseline values following exercise at 5-min post-exercise, MAP, TPR and SV were significantly reduced (all $p \leq 0.05$). No differences between conditions were measured at 5-min post-exercise (all $p > 0.05$) however both CO and HR were significantly reduced at the end of the prolonged treatment delay relative to 5-min post-exercise (all $p < 0.01$) while MAP, TPR and SV remained unchanged.

The plasma volume was significantly reduced to the same extent for all treatment conditions at 5-min post-exercise (short: -9.0 ± 1.3%, moderate: -10.8 ±2.3%; and prolonged: -10.4 ± 2.2%). However a significantly greater reduction was measured at the end of treatment delay for the moderate (-14.5 ± 1.6%; $p = 0.025$) and prolonged (-14.0 ± 1.8%; $p = 0.022$) conditions relative to the short (-9.0 ± 1.3%). The reductions in blood volume measured at 5-min post-exercise were not different between the short (-5.4 ± 0.9%), moderate (-6.6 ± 1.2%), and prolonged (-6.4 ± 1.3%) conditions ($p = 0.497$). Further, a similar reduction in blood volume was measured at the end of the treatment delay period ($p = 0.060$) (i.e., short:-5.4 ± 0.9%, moderate: -9.1 ± 0.9% and prolonged: -8.6 ± 0.9%) conditions.

Cold Water Immersion

The overall cooling rates and time required to reduce both T_{re} and T_{es} to 37.5°C was similar among all conditions (all $p > 0.05$; Table 2). Similarly there were no differences in the cooling rates or the time required to reduce T_{re} and T_{es} by the first degree Celsius or by the second degree Celsius between conditions.

Reductions in MT_{sk} at the beginning of immersion became gradually less as a function of time ($p < 0.00$; Figure 2) and were comparable between all conditions (all $p > 0.05$). Increases in the rate of non-evaporative heat loss reduced as a function of time ($p < 0.01$) at similar rates between conditions (all $p > 0.05$). No differences in the rates of metabolic heat production between conditions was observed at the start of immersion (short: 217 ± 301 W; moderate: 222 ± 21 W; and prolonged: 220 ± 40 W) as well as at the end of immersion (short: 180 ± 37 W; moderate: 219 ± 25 W and prolonged: 257 ± 36 W; all $p > 0.05$) respectively.

Post-immersion Recovery Period

No differences were measured in T_{re} (short: 37.55 ± 0.02°C; moderate: 37.54 ± 0.03°C; and prolonged: 37.50 ± 0.03°C); T_{es} (short: 35.54 ± 0.25°C; moderate: 35.28 ± 0.26°C; and prolonged: 35.29 ± 0.29°C) and MT_{sk} (short: 10.95 ± 0.85°C; moderate: 8.67 ± 1.00°C; and prolonged 8.79 ± 0.78°C) at end of immersion (all $p > 0.05$). Upon exiting the cold water, T_{re} and T_{es} continued to decrease for all conditions reaching a similar point of nadir for the short (T_{re}: 35.95 ± 0.22; T_{es}: 35.12 ± 0.20°C), moderate (T_{re}: 35.61 ± 0.27; T_{es}: 34.97 ± 0.23°C) and prolonged (T_{re}: 35.87 ± 0.20; and T_{es}: 35.02 ± 0.26°C) conditions respectively. The time to reach nadir as defined by T_{re} response was significantly different between the short (17.5 ± 3.0 min) and prolonged (26.7 ± 2.8 min) conditions only ($p=0.008$). In contrast, the time to reach the T_{es} nadir was not different among conditions (short: 3.8 ± 0.7; moderate: 4.4 ± 1.0; and prolonged: 3.2 ± 0.9 min; $p = 0.715$). The post-immersion recovery time as defined by the time required for T_{re} to return to 36.5°C, was similar among all conditions (short: 49.4 ± 20.2 min; moderate: 58.8 ± 19.1 min; and prolonged: 56.5 ± 19.7 min) ($p=0.158$) respectively.

No differences in cardiovascular responses (i.e. CO, HR, SV, MAP and TPR) were measured between conditions at the end of the post-immersion recovery (all $p \leq 0.05$). Values for CO and HR were significantly reduced relative to the end of the treatment delay period for all conditions; however they were still elevated relative to baseline values (all $p \leq 0.05$). Values for MAP, TPR and SV were similar between conditions at the end of the post immersion recovery. Whereas SV returned to baseline resting values MAP and TPR remained significantly reduced albeit attenuated compared to end of treatment delay values with the exception that MAP remained significantly reduced for the short condition relative to the moderate and prolonged conditions (all $p<0.05$).

The percent changes in plasma volume were significantly greater for the moderate (-13.4 ± 1.6%; $p = 0.020$) and prolonged (-14.4 ± 2.4%; $p = 0.024$) conditions relative to the short (-7.4 ± 1.4) condition respectively. A similar pattern of response was measured for blood volume with significantly greater reductions recorded in the moderate (-8.2 ± 0.9%; $p = 0.015$) and prolonged (-8.4 ± 1.1%; $p = 0.023$) conditions compared to the short (-4.2 ± 1.1%) condition. The reductions in body mass observed for the moderate (-2.2 ± 0.3 kg), and prolonged (-2.4 ± 0.5 kg) conditions were significantly greater relative to the short (-1.6 ± 0.3 kg) condition (all $p < 0.01$).

Discussion

In contrast to our study hypothesis, we show that the core cooling rates during CWI in the treatment of exercise-induced hyperthermia were not affected by delays in treatment of up to 40 minutes. We showed that body core temperature was significantly elevated from

baseline values (T_{re} ~36.9; T_{es} ~ 36.8°C) at the end of the treatment delays for T_{re} (~3.0°C) and T_{es} (~2.5°C) measures. This was paralleled by similar marked reductions in MAP (~20 mm Hg) from baseline values (~92 mm Hg). Despite this elevated level of thermal and cardiovascular strain whole body cooling during CWI was similar between conditions. Moreover, core temperature after-drop following CWI and the time taken to recover to baseline resting values was similar among all conditions. Taken together, our findings demonstrate that the application of CWI remains an effective and safe treatment modality even when treatment is delayed by as long as 40 min.

Consistent with previous studies we show that rectal temperature continued to increase (0.10-0.15°C) in the early stages of post-exercise recovery (<5 min), as the residual heat from previously active muscle was gradually transferred to the central core region. By design, we were able to maintain rectal temperature at end exercise values for the duration of each delay period. As such we observed no change in rectal temperature at the end of the 5- and 20-min delay periods and only a 0.39°C reduction at the end of the prolonged 40-min delay condition. In parallel, values for esophageal temperature remained significantly elevated above baseline resting values albeit at lower levels relative to rectal temperature, for all conditions. Interestingly, Gagnon et al. (2012) measured a 1°C reduction in esophageal temperature measured in the first 15-min of recovery following prolonged (120 min) exercise in the heat (42°C). However, Gagnon et al. (2012) did not limit evaporative heat loss during recovery as in the present study. The use of a sleeveless running jacket during recovery in the heat coupled with the time dependant convective transfer of residual heat from previously active muscle to the central core (Kenny et al. 2003), was sufficient to maintain an elevated state of hyperthermia typically observed in untreated EHS victims.

In parallel to the elevated level of hyperthermia recorded in our participants, we showed a pronounced level of cardiovascular strain, as evidenced by marked sustained reductions in arterial blood pressure in the early stages of post-exercise recovery that persisted throughout the delays in treatment. The magnitude of decrease in mean arterial pressure was similar to levels previously reported in victims of EHS. For example, O'Donnell and Clowes (1972) reported marked reductions in MAP values (72 mm Hg) coupled with an elevated HR of 120 beats/min prior to field treatment consisting of ice-water immersion of seven marines suffering from acute EHS. Similarly, Sithinamsuwan et al. (2009) in a retrospective study of twenty-seven patients admitted to the hospital and diagnosed with EHS from 1995 to 2007 reported MAP values of 70 mm Hg combined with an elevated HR of 129 beats/min on arrival at the hospital prior to treatment.

Exercise in the heat without fluid replacement has been shown to elicit marked increases in cardiovascular strain relative to exercise in the heat with fluid replacement, which persists long into the recovery period (Gonzalez-Alonso et al. 1997, Gagnon et al. 2012). In the present study, the substantial reduction in arterial blood pressure observed after the short 5-min delay (-17 mm Hg) is consistent with the reductions reported by Gagnon et al. (2012) following prolonged (120 min) exercise in the heat (42°C) (a decrease of ~20 mm Hg measured for both untrained and endurance trained males) whereby participants also remained in the upright seated posture for a 90 min recovery period in the heat (42°C). However, they reported that in untrained males there was a gradual increase in MAP to near baseline resting levels in the early stages (i.e. 15 min) of the 90 min recovery. While MAP also increased gradually during this same period for the endurance trained males it achieved a plateau at ~15 min which remained significantly reduced (~10 mm Hg) from baseline

resting values for the duration of the recovery. Their findings demonstrated that in the absence of fluid replacement, endurance trained males exhibit an attenuated recovery of MAP following exercise in the heat. In the context of the current study, we recruited individuals who were regularly engaged in physical activity to ensure that they could complete the strenuous exercise protocol. The fitness level of our participants (VO_{2max} of 60 mLO_2/kg/min) was comparable to the endurance trained males (VO_{2max} of 68 mLO_2/kg/min) employed in the study by Gagnon et al. (2012). While the underlying mechanism for this blunted blood pressure recovery in trained males remains unclear, it does demonstrate that these individuals are at greater risk for syncope. It is plausible that the higher level of hyperthermia combined with significant levels of dehydration, albeit similar to the levels of dehydration observed by Gagnon et al. (2012) following exercise, placed a greater overall cardiovascular strain on our participants thereby resulting in the marked sustained reduction in MAP (70 mm Hg) measured even at the end of the prolonged 40-min treatment delay condition. This is further supported by our observations of a sustained elevation in CO and HR coupled with reductions in SV and TPR.

In contrast to our study hypothesis the prolonged exposure of our participants to a sustained and elevated state of thermal and cardiovascular strain lasting up to 40 min following cessation of exercise did not did not alter the effectiveness of the CWI treatment. This is evidenced by our observations of similar core cooling rates and immersion times measured for all treatment conditions. Similarly, there were no differences between conditions in the time taken for the first and second degrees of core temperature reduction as measured from the start of immersion. The second degree of cooling was significantly greater compared to the first degree for rectal temperature which is consistent with the study

by Proulx et al (2003). These differences are attributed to a greater lag time associated in tissue heat transfer observed between the start of immersion and initiation of rectal temperature cooling, thereby resulting in slower temporal response of rectal temperature in the early stages of cooling. Noteworthy, Proulx et al. (2003) reported a ~1.9 fold greater overall core cooling rate (0.35°C/min) relative to the overall core cooling rate observed in the present study (0.17-0.20°C/min) for a similar exercise induced state of hyperthermia (i.e. T_{re} of 40°C). Whereas Proulx et al. (2003) immersed their participants up to neck, which included the arms and hands; we immersed our participants to the nipples only with arms out of the water to accommodate our physiological measurements.

The immersion tub employed in the present study did not permit our participants to be placed in a supine posture similar to the posture employed in the study by Proulx et al. (2003). Rather, our subjects were immersed in the upright seated posture with legs extended. Therefore the differences in surface area exposure combined with postural differences may explain the differences in absolute core cooling rates. Interestingly, Lemire et al. (2009) reported rectal temperature cooling rates of 0.12°C/min for hyperthermic males (39.5°C) immersed in 2.0°C water using a similar posture to the present study. Irrespective of these differences, the rectal temperature cooling rates observed in our study, are similar to or greater than those reported in other studies that cooled hyperthermic individuals with CWI (~2°C) (Costrini 1990, Armstrong et al. 1996, Lemire et al. 2009). Moreover, our observed core cooling rates exceed current guidelines which recommend a cooling rate of 0.10ºC/min when cooling begins immediately (i.e., within 5 min), and not less than 0.15ºC/min when cooling is delayed by 20 to 30 min (Casa et al. 2007). In the context of field studies, our core cooling rates are similar to those reported for 1) EHS patients (0.20ºC/min) who were treated

by immersion of the torso and upper legs in ice water (1-3°C) (Armstrong et al. 1996), and 2) soldiers suffering from EHS (0.15ºC/min) who were subsequently immersed in ice water combined with a vigorous skin massage (Costrini 1990).

A key challenge associated with the use of CWI in the treatment of exercise-induced hyperthermia is reducing the risk of a core temperature after-drop that typically occurs following the removal of the patient from the cold water bath (Proulx et al. 2003, Proulx et al. 2006, Gagnon et al. 2010). The core temperature after-drop has been attributed to conductive and convective heat transfer of cooler blood from the periphery to the core (Gagnon et al. 2010), as well as the transfer of excess amounts of heat above and beyond that which was gained during exercise (Proulx et al. 2006). The magnitude of the reduction in core temperature is dependent upon the duration of the immersion period and the core temperature at which removal from the cold water bath occurs. We hypothesized that the treatment delays would result in longer immersion times due to an attenuated core cooling rate during the immersion period. However, in contrast to our study hypothesis we showed no differences in immersion times and thus in the temperature nadir achieved for both rectal and esophageal temperatures between conditions when participants were removed from the water bath at a rectal temperature of 37.5°C. The lack of differences between conditions in post-exercise hypotension, cooling rates, non-evaporative heat loss and metabolic heat production resulted in similar immersion times and whole body cooling between conditions which therefore resulted in similar post-immersion responses. Our results are consistent with Proulx et al. (2003) who reported a rectal temperature nadir of 35.7°C following 2°C ice-water immersion until rectal temperature reached 37.5°C. Proulx et al. (2003) recommended removing patients from the ice water bath when rectal temperature reaches 38.6°C to ensure

the removal of 100% of the heat gained by exercise and to effectively negate the risks of core temperature after- drop (Proulx et al. 2006). This recommendation was subsequently validated by Gagnon et al. (2010) who reported that cooling previously hyperthermic individuals (T_{re} of 39.5°C) in cold water (2°C) until rectal temperature reached 38.6°C did not result in the overcooling that was observed when the subjects were cooled until their rectal temperature reached 37.5°C. In view of the fact that we observed a similar pattern of response to Proulx et al. (2003) it can be concluded that a similar exit temperature should be used irrespective of the delay in treatment.

Perspectives

Studies show that in EHS victims the risk of adverse outcomes is related to the duration of visceral organ hyperthermia (Bouchama and Knochel 2002, Armstrong et al. 2007). Moreover, length of time that core temperature remains above critical values is the main criterion determining the survival of individuals with EHS (Hubbard et al. 1977). Our study demonstrates that despite the marked and sustained deterioration in cardiovascular function and elevated state of hyperthermia that typically occurs with delays in treatment of EHS victims, CWI remains a safe and effective treatment modality even after a long 40-min delay in the start of treatment. It has recently been argued by some experts (Taylor et al. 2008), that regardless of any delay in treatment, CWI immersion should not be employed because of the potential harmful physiological stress (e.g. cold-shock response, physical discomfort, cold injury, etc.) that it may cause to the individual. However, as demonstrated in this and other studies, CWI provides some of the highest cooling rates while at the same time helping to re-establish near normal resting thermal and cardiovascular function. More importantly, the pattern of response is unaffected by a delay in the start of treatment of as

much as 40 min. Our findings should not be interpreted to suggest that treatment of EHS patients should be delayed in any manner. The rapid cooling of hyperthermic individuals to a near normal resting core temperature must remain the main goal of any treatment strategy and is best achieved with CWI. The cooling process should begin as soon as possible when heat stroke is suspected, and if CWI is not initially available, other modes (wet towels, water spray, etc.) should be utilized until CWI is possible.

In summary we show that despite the prolonged thermal and cardiovascular strain observed with treatment delays up to 40 min in individuals rendered hyperthermic through prolonged exercise in the heat, CWI resulted in similar core cooling rates. Our findings demonstrate that CWI is a safe and effective treatment modality even when treatment is delayed up to 40 min.

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Table 1 – Baseline values for rectal (T_{re}), esophageal (T_{es}), cardiac output (CO), mean arterial pressure (MAP), total peripheral resistance (TPR), heart rate (HR), and stroke volume (SV) and their corresponding changes from baseline at 5-min post-exercise, end of treatment delay, and end of post-immersion recovery.

	Baseline	5 min Post-Exercise	Treatment Delay	Post-Immersion Recovery
T_{re} (°C)				
Short	36.91 ± 0.10	+3.16 ± 0.13*	+3.16 ± 0.13*	-0.42 ± 0.09§
Moderate	36.86 ± 0.07	+3.29 ± 0.08*	+3.09 ± 0.11*	-0.41 ± 0.14§
Prolonged	36.84 ± 0.09	+3.25 ± 0.11*	+2.77 ± 0.09*†‡	-0.33 ± 0.13§
T_{es} (°C)				
Short	36.82 ± 0.10	+2.97 ± 0.20*	+2.97 ± 0.20*	-0.11 ± 0.10§
Moderate	36.88 ± 0.05	+3.23 ± 0.13*	+2.63 ± 0.18*†	+0.20 ± 0.12§
Prolonged	36.72 ± 0.10	+3.03 ± 0.20*	+1.86 ± 0.10*†‡	+0.28 ± 0.20§
CO (L/min)				
Short	6.0 ± 0.3	+5.2 ± 0.9*	+5.2 ± 0.9*	+1.9 ± 0.5*§
Moderate	5.8 ± 0.4	+4.8 ± 0.6*	+4.1 ± 0.4*	+1.5 ± 0.4§
Prolonged	5.8 ± 0.3	+5.3 ± 0.7*	+3.8 ± 0.4*†	+1.7 ± 0.2*§
HR (beats/min)				
Short	60 ± 3.6	+77 ± 5.5*	+77 ± 5.5*	+17 ± 3.2*§
Moderate	61 ± 3.6	+81 ± 2.5*	+76 ± 3.7*	+13 ± 2.8*§
Prolonged	61 ± 3.5	+79 ± 4.7*	+60 ± 2.8*†	+19 ± 4.9*§
SV (mL)				
Short	100 ± 8.8	-16 ± 9.7*	-16 ± 9.7*	+7± 7.8
Moderate	96 ± 5.5	-21 ± 3.3*	-24 ± 3.9*	+5 ± 7.5
Prolonged	95 ± 4.7	-15 ± 5.1*	-16 ± 3.4*	+1 ± 8.0
MAP (mm Hg)				
Short	92 ± 1.6	-17 ± 2.4*	-17 ± 2.4*	-11 ± 1.4*
Moderate	92 ± 1.8	-17 ± 2.3*	-18 ± 2.4*	-7 ± 2.9*§
Prolonged	92 ± 4.3	-20 ± 11.8*	-22 ± 4.1*	-6 ± 4.9*§
TPR (mm Hg/L/min)				
Short	15.2 ± 0.7	-8.5 ± 0.6*	-8.5 ± 0.6*	-5.6 ± 0.9*§
Moderate	15.0 ± 0.7	-8.2 ± 0.3*	-7.1 ± 0.5*	-4.1 ± 0.9*§
Prolonged	15.4 ± 0.8	-9.1 ± 0.8*	-8.2 ± 0.8*	-4.5 ± 0.5*§

Note: The values for baseline measures are in thermoneutral (~23°C) ambient conditions. Values are presented as mean ± SE. * indicates significant difference from baseline; † indicates significant difference from 5 min post-exercise; ‡ indicates significant difference from the short condition, § indicates significant difference from treatment delay (all $p \leq 0.05$).

Table 2 – Core cooling rates for both rectal and esophageal temperatures for different core temperature intervals during cold water immersion after delays in treatments.

		Cooling Rates, °C/min		
	Pre-Immersion ($T_{pre\text{-}imm}$°C)	**1st °C Cooling ($T_{pre\text{-}imm}$-1°C)**	**2nd °C Cooling [($T_{pre\text{-}imm}$-1°C)-1°C]**	**Immersion Period (Until 37.5°C)**
		Rectal Temperature		
Short	40.08 ± 0.32	0.18 ± 0.02	0.24 ± 0.02*	0.21 ± 0.03
Moderate	39.92 ± 0.40	0.14 ± 0.01	0.21 ± 0.01*	0.17 ± 0.01
Prolonged	39.57 ± 0.29†	0.15 ± 0.02	0.23 ± 0.01*	0.17 ± 0.01
		Esophageal Temperature		
Short	39.58 ± 0.25	0.45 ± 0.06	0.55 ± 0.07	0.47 ± 0.03
Moderate	39.30 ± 0.39	0.40 ± 0.06	0.53 ± 0.06	0.45 ± 0.01
Prolonged	38.51 ± 0.41†‡	0.43 ± 0.06	0.45 ± 0.09	0.41 ± 0.03

Note: The pre-immersion ($T_{pre\text{-}imm}$) rectal and esophageal temperatures are the temperature values following the short (5-min), moderate (20-min) and prolonged (40-min) treatment delay periods immediately prior to cold water immersion. The first degree Celsius drop in core temperature is the $T_{pre\text{-}imm}$ - 1°C for each respective condition for both rectal and esophageal temperatures. Further the second degree Celsius drop in core temperature is the ($T_{pre\text{-}imm}$ - 1°C) - 1°C. Values are means ± SE. *Indicates significant difference from 1st degree cooling; †indicates significant difference from the short condition; ‡indicates significant difference from the moderate condition (all $p < 0.05$).

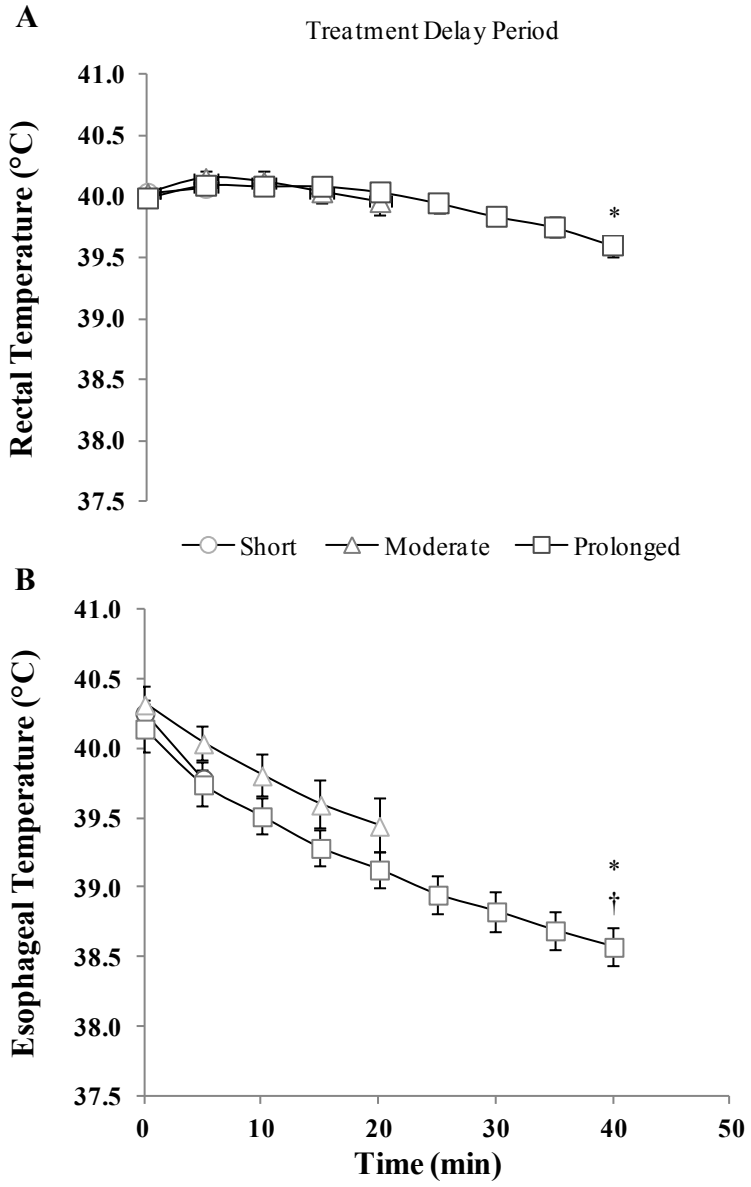

Figure 1 – Rectal temperature (A) and esophageal temperature (B) responses during the treatment delay periods after exercise-induced hyperthermia. Values are presented as mean ± SE for the short (5-min) (○), moderate (20-min) (Δ), and prolonged (40-min) (□) treatment delay conditions. The values at the 0 time point are the values at the end of exercise for each condition. Values are also presented for the end of each respective delay period. * Significantly different from the short condition; † significantly different from the moderate condition ($p < 0.05$).

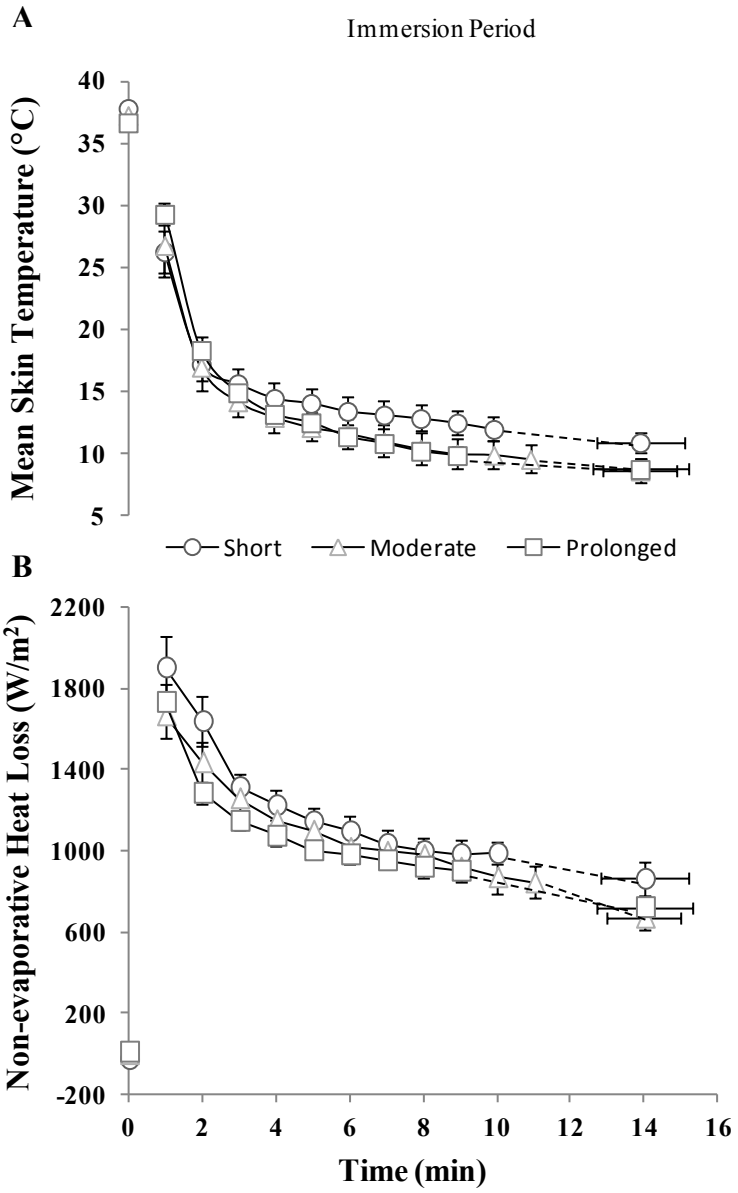

Figure 2 – Mean skin temperature (A) and rate of non-evaporative heat loss (B) during cold water immersion (2°C) after exercise-induced hyperthermia followed by subsequent treatment delays. Values are mean ± SE for the short (5-min) (○), moderate (20-min) (Δ), and prolonged (40-min) (□) treatment delay conditions. The values at the 0 time point are the values at the end of each treatment delay (i.e. pre-immersion values). Data is presented for the immersion time periods common to all conditions and at end immersion. The dashed lines represent mean values for the end of immersion for each participant.

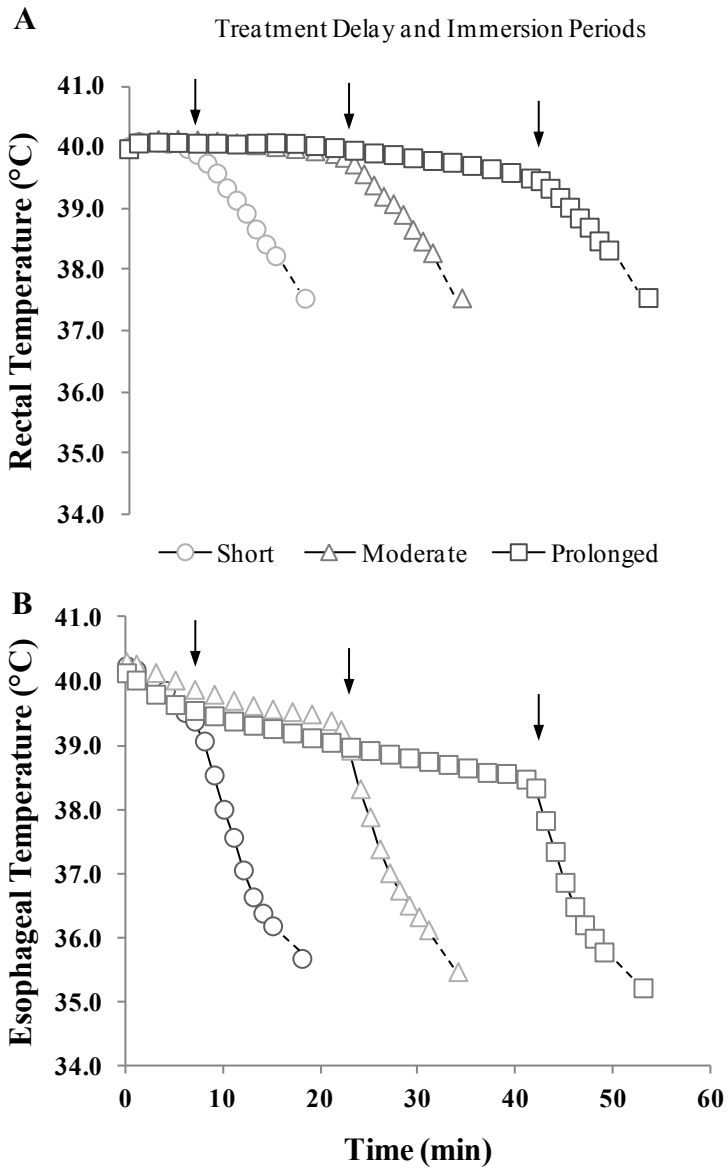

Figure 3 –Rectal (A) and esophageal (B) temperatures during post-exercise recovery (i.e. treatment delay periods and subsequent cold water immersion (2°C)) after exercise-induced hyperthermia. Values are mean ± SE for the short (5-min) (○), moderate (20-min) (Δ), and prolonged (40-min) (□) treatment delay conditions. The values at the 0 time point are the values at the end of exercise for each condition. Data is presented for the immersion time periods common to all participants in each condition as well as at the mean core temperature value (i.e. both rectal and esophageal) at end immersion. The mean core temperature value at the end of immersion is identified at the average immersion time for each condition and is joined by a dashed line. The arrow (↓) indicates the start of immersion for each respective treatment delay condition.

PART THREE: GENERAL CONCLUSIONS OF THE THESIS

GENERAL CONCLUSIONS OF THE THESIS

This thesis work was directed at examining the influence of prolonged exercise-induced hyperthermia in a heat stress environment on subsequent treatment (via cold water immersion) and post treatment recovery. This study is the first to examine the effects of delays in treatment up to 40 min in a heat stress environment following hyperthermia rendered by exercise in the heat. This includes the study of thermal and cardiovascular responses during delays in treatment, cold water immersion treatment and post-immersion recovery. More specifically, we studied the core temperature, cardiac output and mean arterial pressure during treatment delays up to 40 min. We also examined the effects of prolonged hyperthermia in a heat stress environment on core cooling rates, time to cool, the post cooling after drop and post-immersion recovery on these variables.

An important finding in this study is that delays in treatment in a hot environment after exercise in the heat resulted in an altered thermoregulatory response. Typically, during recovery from exercise rectal temperature remains elevated but demonstrates a gradual decay throughout the recovery period (Thoden et al. 1994) lasting up to 60 min or longer. Esophageal temperature however generally displays a rapid reduction within the first 15 min after the cessation of exercise, followed by a sustained plateau of ~0.4-0.7°C above baseline resting values during a similar recovery period (Thoden et al. 1994). We report that rectal temperature continued to increase despite the cessation of exercise to an apex at ~4 min post-exercise followed by subsequent temperature decay. Rectal temperature values were reduced to end exercise values following 20 min of post exercise recovery; thereafter rectal temperature continued to decay. Esophageal temperatures remained significantly elevated above baseline resting values at the end of each treatment delay demonstrating sustained hyperthermia. It is noteworthy that the

esopahgeal temperatures decayed gradually throughout the post-exercise recovery periods in contrast to previous studies (Thoden et al. 1994, Gagnon et al. 2012). Irrespective of the post-exercise core temperature responses it is evident from our findings that treatment delays in individuals with exercised-induced hyperthermia prolongs the time that both the visceral organs (as assessed by T_{re}) (Gagnon et al. 2010) and central nervous system (as assessed by T_{es}) (Taylor et al. 2008) remain hyperthermic effectively increasing the risk of adverse outcomes from EHS.

The most significant finding from this study is that despite the prolonged cardiovascular and thermal strain endured by treatment delays in hyperthermic individuals the cooling properties of CWI were sufficient to rapidly reduce core temperatures. This is evidenced by similar core cooling rates and immersion times coupled with similar post-immersion recovery responses between all conditions. Furthermore CWI facilitated the re-establishment of cardiovascular variables to near normal resting levels without observation of an ill effects suffered by participants. Therefore, CWI is a safe and effective treatment modality that can be used by health care practitioners for individuals suffering from EHS when treatment has been delayed up to 40 min.

In summary, our findings provide new insight into the thermoregulatory and cardiovascular responses during delays in treatment and subsequent recovery in individuals who have been rendered hyperthermic by exercise in the heat. Our results demonstrate that cold water immersion is a safe and effective treatment modality for individuals who experience prolonged exercise induced hyperthermia up to 40 minutes. Additionally, cold water immersion treatment did not result in any cardiovascular complications during treatment and subsequent recovery. Future research should focus on examining sudomotor activity and skin blood flow responses as

well as the effects of dehydration during and following delays in treatment to further understand the thermoregulatory response.

PART FOUR: REFERENCES

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PART FIVE: APPENDIX

5.0 Additional Graphs

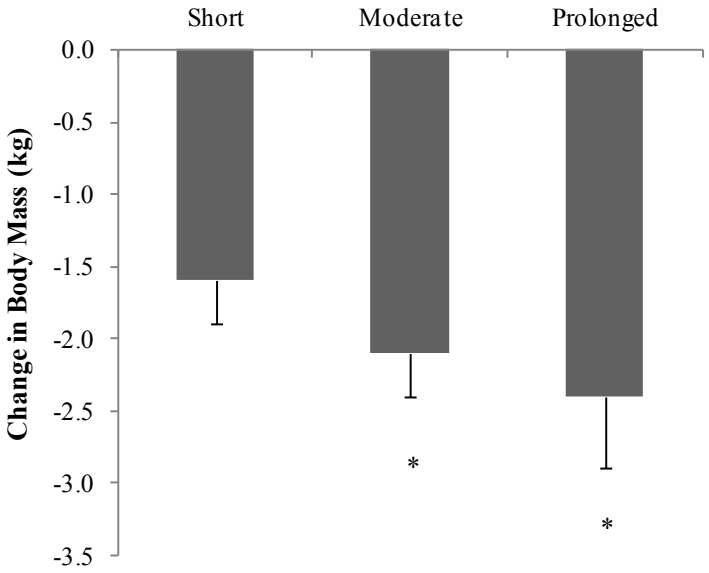

Figure 4 – Reductions in body mass after exercise-induced hyperthermia, delays in treatment, cold water immersion treatment and post-immersion recovery. Values are presented as mean ± SE for the short (5-min), moderate (20-min), and prolonged (40-min) treatment delay conditions. * Significantly different from the short condition.

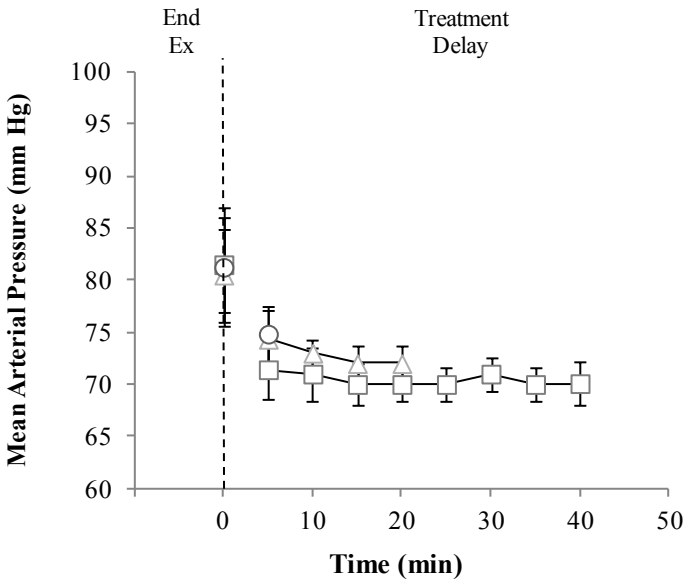

Figure 5 – Mean arterial pressure responses during the treatment delay periods after exercise-induced hyperthermia. Values are presented as mean ± SE for the short (5-min) (○), moderate (20-min) (Δ), and prolonged (40-min) (□) treatment delay conditions.

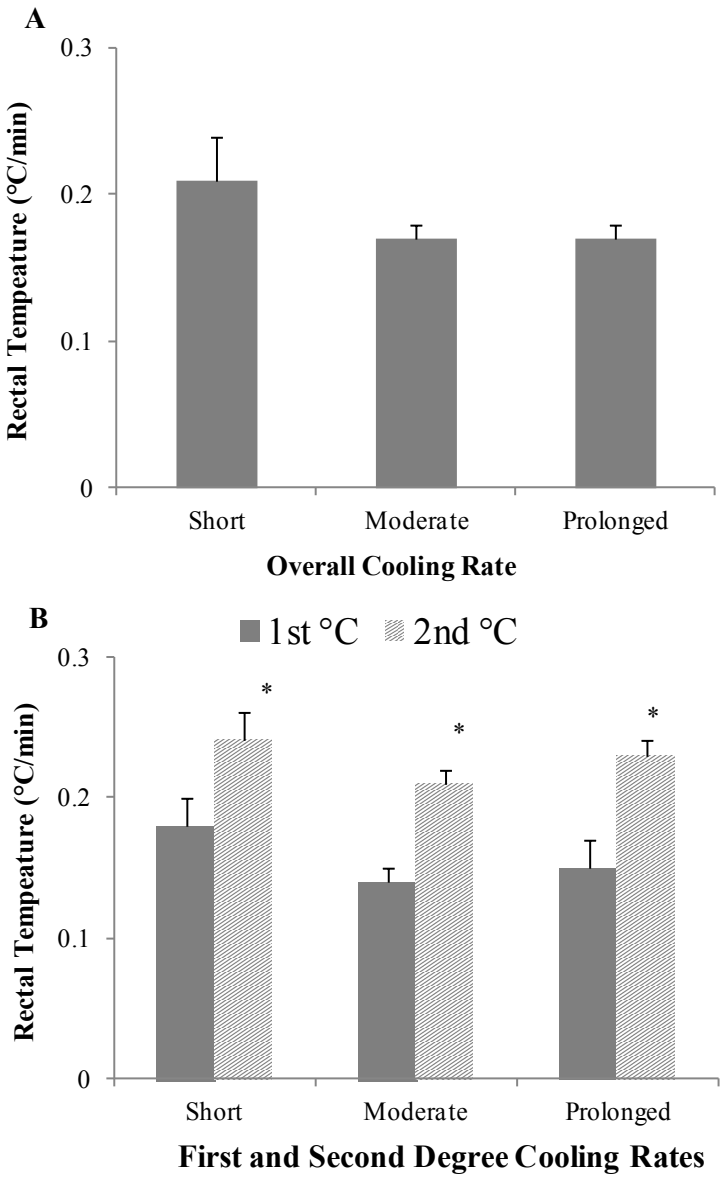

Figure 6 – Rectal temperature cooling rates for the overall (A) immersion period as well as the first (1st) and second (2nd) degree Celsius reduction in temperature (B) after exercise induced hyperthermia and subsequent treatment delays. Values are presented as mean ± SE for the short, moderate and prolonged treatment delay conditions. *Significant difference from the 1st degree reduction in temperature.

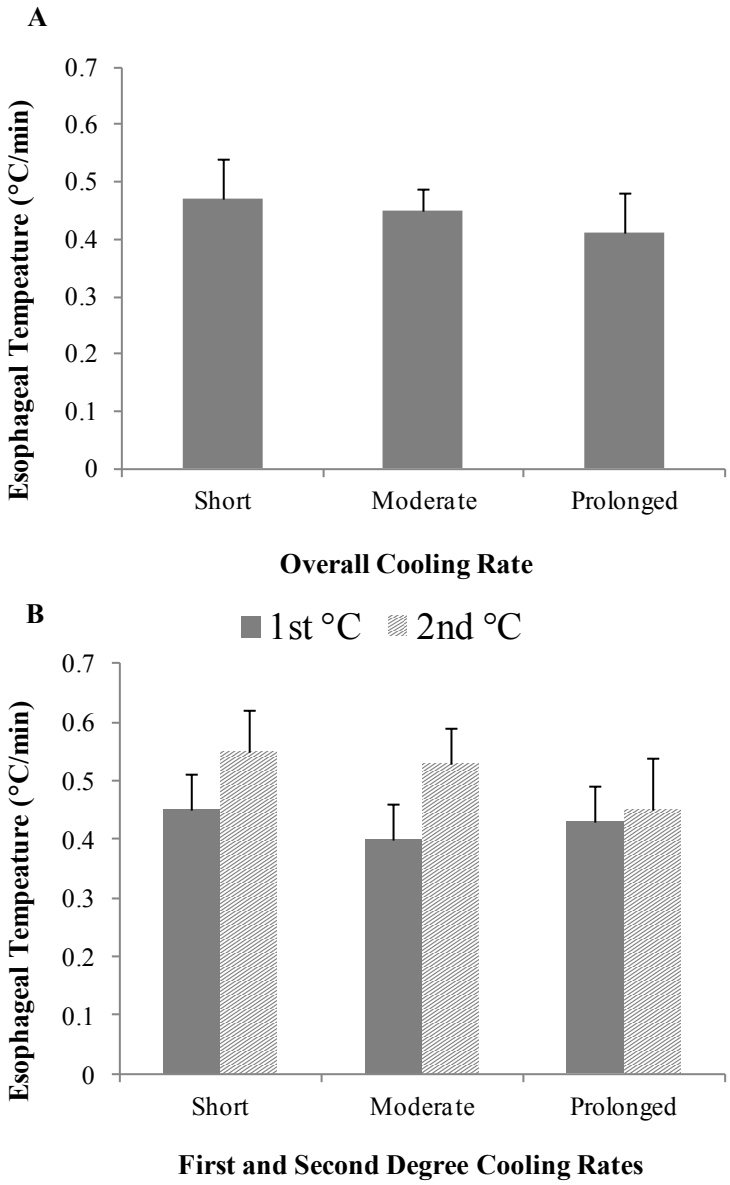

Figure 7 – Esophageal temperature cooling rates for the overall (A) immersion period as well as the first (1^{st}) and second (2^{nd}) degree Celsius reduction in temperature (B) after exercise induced hyperthermia and subsequent treatment delays. Values are presented as mean ± SE for the short, moderate and prolonged treatment delay conditions.

5.1 Background Information and Informed Consent

Cardiovascular and Thermal Response during Incremental levels of Exercise-Induced Hyperthermia, and after Delays in Treatment Time

Investigators:

Dr. Glen Kenny (Ph.D.), Professor

Mr. Mark Carlson[1], Ms. Jill Stapleton and Dr. Heather Wright

University of Ottawa, School of Human Kinetics

Background

Many occupational and recreational environments, such as firefighting, mining, and sporting competitions, lead to increases in core temperature due to exercising in the heat. Treatment for exercise-induced hyperthermia involves lowering core body temperature preferably through cold water immersion immediately however in these occupational and field settings time to treatment can be upwards of 45 min. Of particular importance is determining whether recovery from exercise-induced heat stress differs as a function of the time at which treatment is applied. In addition, in these same occupational and recreational settings, the increases in core temperature that individuals experience can vary due to numerous factors (i.e. intensity of exercise, ambient temperature conditions, etc.) Thus, it is critical to also examine the effects of different levels of hyperthermia and how to best provide recovery to reduce the severity of heat related injuries.

Purpose

The purpose is directed at advancing our knowledge of the thermal, cardiovascular, and neuroendocrine responses associated with the onset and subsequent recovery from exercise-induced hyperthermia. Specifically, studies will be directed at evaluating the effects of delayed time to treatment (5 min, 15 min, and 30 min) on two methods of recovery (temperate and cold water immersion) from exercise-induced hyperthermia (Study A). Further, we will examine how different levels of hyperthermia influence this response (Study B).

Information obtained from your participation in our study will help us increase our understanding of the health risks associated with physical work performed in the heat. By increasing our understanding of how individuals respond to work in the heat and recovery from heat stress, it will be possible to understand what steps and precautions may be taken to avoid exertional heat-related injuries. In the event that a heat-injury occurs we will develop a better understanding of the appropriate treatment strategy. This study is funded by the Natural Sciences and Engineering Research Council.

Subject profile

To be a participant you must be a healthy (no history of respiratory, metabolic, cardiovascular, blood pressure disease, and/or diabetes, and not currently on any medication related to these conditions) adult, aged between 18 and 45 years. Women who are pregnant or expect to become pregnant will also be excluded. You must be physically active, such that you are physically active a minimum of three to four times a week at a moderate to hard intensity for at least 30 minutes. If you agree to participate in this study, you will be required to participate in one familiarization session, and opt to participate in Study A (6 experimental sessions) and/or B (2 experimental sessions), with sessions to be conducted on different days.

Compensation

You will be compensated for parking and meals for each experimental trial in which you partake.

Familiarization session

Both the familiarization session and the experimental sessions will take place in at the Human Environmental Physiology Laboratory located on the main campus at the University of Ottawa. This session will take approximately 1 hour to complete and confirm your eligibility. During this familiarization session, we will review all procedures with you of the entire protocol. In addition, you will be introduced to all of the equipment and measuring devices that will be used during the experimental sessions (see below). We will give you the opportunity to read the 'Background Information and Informed Consent' document (current document). If you agree to participate in the study, we will ask you to sign the informed consent (p. 8 below) and complete a *Physical Activity Readiness Questionnaire (Par-Q)* and an *American Heart Association/American College of Sports Medicine Health/Fitness Facility Pre-participation Screening Questionnaire*

(questionnaires attached). These questionnaires are standard questionnaires that have been developed to help us evaluate your readiness for exercise and are also used to assist us in evaluating your general physical health and level of physical activity. We will also complete some basic measurements including height, mass, and percent body fatness (underwater weighing). For the underwater weighing, you will be asked to wear a bathing suit, enter the tank, and situate yourself on the hanging chair. You will be asked to immerse yourself completely under water for 5 seconds. Five trials will be conducted to obtain accurate results, where you will be a few minutes to relax between trials. In addition, a single venipuncture will be done to collect blood for baseline hematologic, osmolality, and neuroendocrine markers. Following these measures, you will be asked to perform a maximum oxygen consumption test on a motorized treadmill. This will consist of running at a selected speed (6-8 mph) while the grade of the treadmill is increased by 2% every two minutes until you can no longer continue (Approx. 8-12 min).

Experimental session

Upon arrival to the laboratory, you will change into athletic clothing (t-shirt, shorts, socks, and running shoes), followed by an instrumentation period. Once all the equipment and probes (see below) are in place and functioning, baseline data will be collected at an ambient temperature of 25°C for 15 minutes.

In preparation for the experimental trials, you will be asked to abstain from alcohol, caffeine and severe or prolonged physical activities for 24 hours prior to all sessions. It is highly recommended that you avoid eating for at least two hours before the trial.

The experimental trials are conducted under the responsibility of a physician. All procedures considered a controlled act will be performed by, or under, the delegation of a nurse or by a physician for those procedures which can only be performed by a physician (The College of Physicians and Surgeons of Ontario, the Delegation of Controlled Acts, S.O. 1991, Chapter 18, amended 2006; and/or the College of Nurses of Ontario, Legislation and regulation, subsection RHPA, scope of practice, controlled acts model, 2005).

Study A will consist of 6 experimental sessions, each lasting approximately 4-5 hours. Following baseline data collection, you will be transferred to an environmental chamber (40°C, 30% relative humidity [R.H.]) where you will run on a treadmill at 65% of VO_{2peak} exercise intensity, leading to an increase in rectal temperature. Upon reaching a rectal temperature of

40.5°C, you will be treated after a delay of either: 5 min, 20 min, or 40 min, by temperate or cold water immersion. During delays to treatment, you will remain seated quietly in the environmental chamber (40°C, 30% R.H.). During recovery you will be cooled in a tub of either temperate (26°C) or cold (2°C) water until rectal temperature returns to resting levels. Thus, there will be 6 experimental sessions: 1) Immediate (5 min) treatment with temperate water (26°C), 2) Immediate (5 min) treatment with cold water (2°C), 3) 20 min delayed treatment with temperate water, 4) 20 min delayed treatment with cold water, 5) 40 min delayed treatment with temperate water, and 6) 40 min delayed treatment with cold water.

Study B will consist of 2 experimental sessions, each lasting approximately 4-5 hours. Following baseline measurements, you will be transferred to an environmental chamber (40°C, 30 % R.H.) where you run on a treadmill at 65% VO_{2peak} leading to an increase in rectal temperature. Upon reaching a rectal temperature of 38.5°C you will sit quietly for 5 min for a HR reading, following the reading you will resume running and repeat the process until achieving rectal temperatures of 39.5°C and 40.5°C respectively. Following the HR measurement taken upon reaching a rectal temperature of 40.5°C participants will be treated in either a temperate water bath (26°C) or a cold water bath (2°C) until rectal temperatures return to resting levels. Thus there will be 2 experimental sessions 1) treatment with temperate water (26°C), 2) treatment with cold water (2°C).

The following instruments will monitor and record your physiological responses during the experimental sessions:

***Esophageal probe*:** In order to monitor central body temperature, the researcher will insert a flexible esophageal temperature probe (2 mm in diameter) through one of your nostrils, during which time you will be asked to swallow sips of water. The tip of the probe, once fully inserted in your esophagus (swallowing tube), will rest at the level of the heart. There can be mild discomfort and mild gagging reflex from swallowing the probe. However, this sensation passes within 5-10 seconds.

***Rectal probe*:** You will be asked to insert a flexible probe though the anus into the rectum (10-12 cm). Proper instruction will be given to you on the placement of the rectal probe. A marker is placed on the rectal probe using sterile surgical tape. The subject inserts the probe until the tape reaches the anal skin surface. The insertion of the rectal probe may cause some mild discomfort and minor irritation; however, this sensation soon passes. This probe provides the researcher

with an indication of the amount of heat stored in your body. You should be aware that there is some minimal risk associated with the insertion of a rectal probe. With the insertion, there is a risk of perforation of the rectum, and this may cause some discomfort and minor irritation. However, proper instruction will be given to you on the placement of the rectal probe to ensure your safety and comfort. You will be responsible for the insertion of this probe.

***Skin probes*:** Twelve skin probes will be taped to the skin surface with hypoallergenic tape. These probes give an indication of skin temperature and heat loss from the skin surface. Some hair may need to be shaved (by the use of disposable razors) in order to secure the probes adequately to the skin surface. Some discomfort may be experienced upon removing the tape.

***Sweat capsule*:** A small plastic capsule will be taped to the back of the shoulder (upper back). This capsule picks up humidity from the skin and provides an indication of sweat rate.

***Blood pressure*:** Blood pressure will only be monitored before and after the exercise period. Blood pressure will be monitored by a Finapres fingertip blood pressure monitor (Finapres Medical Systems), as well as manually at pre-selected intervals with a sphygmomanometer and a stethoscope. You will feel slight pressure on your finger while blood pressure is being taken.

***Blood flow*:** A flexible laser probe will measure skin blood flow non-invasively at the mid-forearm. This measuring device does not result in any discomfort or residual medical effects.

***Oxygen consumption*:** An automated metabolic cart (MOXUS Modular Metabolic System) will be used to assess oxygen consumption. You will be required to wear a breathing valve connected to the metabolic cart and a nose plug for the majority of the study.

***Heart rate*:** Heart rate will be monitored by a strap placed around the chest (Polar Vantage^{TM} heart rate monitor).

***Cardiac output*:** Cardiac output will be measured using a non-invasive inert gas re-breathing technique (Innocor, Lindvedvej 75, DK-5260 Odense S, Denmark). You will be required to breathe minute quantities of a blood soluble and insoluble gas through a re-breathing valve for a

short period (approximately 15 seconds). Cardiac output measurements will be taken 5 times during each experimental trial 1) at the end of baseline data collection; 2) at the end of rest; 3) 5 minutes post exercise; 4) immediately prior to treatment; and 5) post treatment when the participant's T_{re} returns to baseline.

Blood samples: Venous blood samples will be collected through an indwelling I.V. plastic catheter in a superficial vein (i.e. cubital or cephalic veins), with an extension line. Blood samples (approximately 10 mL) will be drawn 7 times during each experimental trial: 1) Baseline (prior to entering the heat), 2) upon reaching a core temperature of 39.0°C, 3) Immediately at the end of the heat stress exposure/exhaustion (40.0°C core temperature, prior to entering ambient temperature), 4) Beginning of recovery (5 minutes post-heat), and 5) at core temperatures of 39.0°C, 38.5°C, and 38.0°C (~ pre, middle, and end of recovery) during recovery. Blood will be drawn into sterile plastic syringes and transferred immediately into serum with no additive and plasma K_2EDTA 5.4 mg BD Vacutainer® tubes. Non-additive blood will sit for 20 minutes to clot before centrifugation, whereas the EDTA blood will be mixed by inversion and centrifuged immediately. Following centrifugation, serum and plasma aliquots will be transferred into polypropylene tubes, frozen at -20°C, and stored at -70°C until analyzed. An EDTA blood tube will be used for immediate hematologic analyses. The blood samples will be analyzed for various neuroendocrine/immune markers such as HSP72, Epinephrine, Aldosterone, Growth Hormone, Serotonin, and Prolactin, and will be discarded following the analyses. Blood samples will be drawn by qualified personnel (phlebotomy and catheterisation) under the delegation of a medical authority.

Risks and discomforts

All research staff are trained and CPR, and in the event of a health related emergency, we have emergency phones located in the laboratory for immediate contact with University emergency response (University Protection Office).

Physical activity: There are some physical risks associated with any form of exercise. There is essentially no major risk for young, healthy, active people while performing the submaximal exercises. Some effects of maximal exercise testing are nausea, dizziness, fainting, abnormal blood pressure, chest pain, and leg cramps. For the maximal and experimental exercise sessions, the 'Guidelines for Graded Exercise Testing and Exercise Prescription' (by the American College of Sports Medicine) indicate that for men under 40 years of age and women under 50 years of age, with no symptoms or risk factors for cardiovascular disease, the presence of a physician during the test is not required. The incidence of cardiac arrest during maximal exercise

tests is 1 in 10 000 tests. Participants may stop at any time during these tests. All tests will be conducted under standardized conditions for human exercise experiments as laid out by the Canadian Society for Exercise Physiology and the American College of Sports Medicine.

Temperature probes: Perforation of the esophagus, oral, and/or nasal cavities, and the rectum, can occur during insertion of the esophageal and rectal probes, respectively (potentially causing inflammation and infection). Perforation of the esophagus, oral, and/or nasal cavities, as well as the rectum, is very rare and no such incident has ever occurred in this laboratory. The risk of transmission of infectious disease is negligible as each subject has their own sterile probes that will be disposed of once all tests have been completed.

Elevation of core body temperature: There are certain risks that accompany exercise-induced dehydration due to marked elevations in core temperature. These include: headache, extreme weakness, dizziness, nausea, hyperventilation, hypotension, confusion, diarrhoea, vomiting, and loss of consciousness. During all experimental protocols, you will be monitored closely by the research assistant. Further, core body temperatures will be recorded and examined continuously during the experimental trials, and exercise will be terminated if you reach 40.0°C rectal temperature. Additionally, during the experimental protocols, a circulating cold water bath will be available if needed to rapidly cool you. If you become light headed or dizzy, exercise will be terminated and a mat will be readily available, in an adjacent room maintained at a comfortable ambient temperature, where you will be laid in the supine position, cooled with cold towels, and given a commercially available sports drink (Gatorade®) in order to rehydrate and maintain blood sugar.

Blood samples: There is a small risk of infection during and following a venipuncture, however all venipuncture techniques will be performed under standard care procedures by qualified personnel under the delegation of a medical authority. To minimize the occurrence of an infection, the affected region will be cleaned with isopropyl alcohol and sterile gauze pads prior to the venipuncture, followed by a period of local pressure and sterile bandage application. Blood hematologic analysis will be done by the Gamma-Dynacare laboratory at the University of Ottawa Health Services Clinic on 100 Marie Curie Street, Ottawa, ON, KIN 6N5. All blood samples are discarded and properly destroyed by Gamma-Dynacare laboratories immediately upon completion of the hematologic analysis. Neuroendocrine blood samples will be analyzed within the laboratories of the School of Human Kinetics at the University of Ottawa.

A first aid kit is readily available in the laboratory if required for any session.

Anonymity and Confidentiality

All raw data will be stored using alphanumeric coding system. As such, no one will be able to identify you as your name will not appear on these files. Data will be kept in the Laboratory of Human Bioenergetics and Environmental Physiology in locked file cabinets and only the researchers mentioned above will have access to your data.

No records bearing your name will leave the institution. You are encouraged to request and discuss the results of your personal data and the experimental trials at any time. The results of the familiarization session (aerobic fitness and body composition) will be available to you upon completion of the study.

The data collected in this study will be published in scientific journals. The data will kept for a period of 10 years post-publication and will subsequently be destroyed by the physical resources service of the University of Ottawa.

For the entire duration of the study, it is fully understood that you may refuse to participate or withdraw from the study at any time and without question. You may also withdraw from participating when you are in the thermal chamber or at any point during either the exercise or recovery period.

INFORMED CONSENT OF PARTICIPANT

Research involving human subjects requires written consent of the participants.

I, _____, hereby volunteer to participate as a subject in the study entitled **"Cardiovascular and Thermal Response during Incremental levels of Exercise-Induced Hyperthermia and after Delays in Treatment Time"** and can opt to participate in Study A and/or Study B (see below). I have read the information presented in the above background information and I have had the opportunity to ask questions to the investigators. I understand that my participation in this study, or indeed any research, may involve risks that are currently unforeseen.

I recognize that there will be no direct benefit to me from my participation in this study (besides receiving an aerobic fitness and body composition evaluation).

I have been given a copy of this Background Letter and Consent Form for me to keep.

Study A:

Signature of participant: _____ Date: _____

Signature of Researcher: _____ Date: _____

Study B:

Signature of participant: _____ Date: _____

Signature of Researcher: _____ Date: _____

5.2 Ethical Approval Notice

File Number: H01-10-02 **Date (mm/dd/yyyy):** 03/15/2013

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Glen	Kenny	Health Sciences / Human Kinetics	Principal Investigator
Mark	Carlson	Health Sciences / Human Kinetics	Co-investigator
Matthew	Coutsos	Health Sciences / Human Kinetics	Co-investigator
Daniel	Gagnon	Health Sciences / Human Kinetics	Co-investigator
Heather	Wright	Health Sciences / Human Kinetics	Co-investigator
Brian	Friesen	Health Sciences / Human Kinetics	Student Researcher
Jill	Stapleton	Health Sciences / Human Kinetics	Research Assistant

File Number: H01-10-02

Type of Project: Professor

Title: Cardiovascular and Thermal Response during Incremental Levels of Exercise-induced Hyperthermia, and After Delays in Treatment Time

Renewal Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
03/16/2013	03/15/2014	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:
N/A

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