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GRADE / DEGREE:	**ANNÉE D'OBTENTION / YEAR GRANTED**
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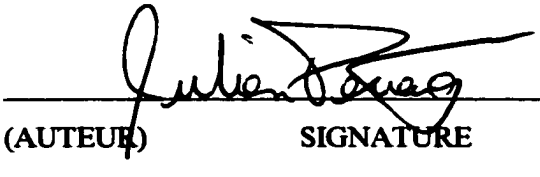

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FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES

FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

PÉRIARD, Julien

AUTEUR DE LA THÈSE - AUTHOR OF THESIS

M.A. (Human Kinetics)

GRADE - DEGREE

School of Human Kinetics

FACULTÉ, ÉCOLE, DÉPARTEMENT - FACULTY, SCHOOL, DEPARTMENT

TITRE DE LA THÈSE - TITLE OF THE THESIS

The Effect of Exercise Intensity on Post-Exercise Skin Blood Flow Control

Francis Reardon and Glen Kenny

DIRECTEUR DE LA THÈSE - THESIS SUPERVISOR

EXAMINATEURS DE LA THÈSE - THESIS EXAMINERS

E. Doucet

D. Prud'homme

J.-M. De Koninck, Ph.D.

LE DOYEN DE LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES

SIGNATURE

DEAN OF THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

The Effect Of Exercise Intensity On Post-Exercise Skin Blood Flow Control

by

JULIEN PÉRIARD

B.Sc., B.Ed. University of Ottawa, 1999, 2000

THESIS

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ABSTRACT

Exercise induces a residual post-exercise increase in the core temperature threshold at which cutaneous vasodilation and sweating begins. The hypothesis that exercise intensity causes a parallel increase in the post-exercise onset threshold for cutaneous vasodilation mediated by an attenuation of active vasodilator activity, was tested in nine subjects. The effect of exercise intensity on the esophageal temperature threshold for the onset of sweating was also evaluated. Esophageal temperature was monitored as an index of core temperature while sweat rate was measured using a ventilated capsule placed on the upper back. Increases in forearm skin blood flow and mean arterial blood pressure were measured and used to calculate cutaneous vascular conductance at two superficial sites, one with intact α-adrenergic vasoconstrictor activity and one infused with bretylium tosylate. On four separate days, subjects either remained seated for 35 min or performed 15 min treadmill running at 55, 70 or 85% VO_2max followed by 20 min seated recovery. A liquid conditioned suit was used to increase mean skin temperature until cutaneous vasodilation and sweating occured. It is concluded that intensity of exercise has a prolonged residual effect on the post-exercise vasomotor and sudomotor response by increasing the esophageal temperature at which onset of vasodilation and sweating occurs. Furthermore, the post-exercise increase in onset threshold for vasodilation is likely caused by an attenuation of active vasodilator activity modulated by baroreceptor reflexes in response to post-exercise hypotension.

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TABLE OF CONTENTS

ABREVIATIONS

CVC	cutaneous vascular conductance
CVC_{max}	maximum cutaneous vascular conductance
HUT	head-up tilt
LBNP	lower body negative pressure
LBPP	lower body positive pressure
MAP	mean arterial pressure
PEH	post-exercise hypotension
T_{amb}	ambient temperature
T_c	core temperature
T_{es}	esophageal temperature
Th_{SW}	the T_{es} at onset of sweating
Th_{VD}	the T_{es} at onset of skin vasodilation
T_{loc}	local skin temperature
T_{sk}	mean skin temperature
T_{suit}	temperature of the liquid in the liquid conditionned suit
SkBF	skin blood flow
VO_2max	maximum oxygen uptake

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

1.0 Introduction

Several exercise studies have examined the warm thermal responses of sweating (Johnson and Park, 1981; Lopez et al., 1995; Tam et al., 1978) and cutaneous vasodilation (Kellogg et al., 1993; Kellogg et al., 1991b; Smolander et al., 1991; Taylor et al., 1988). However, little is known about the post-exercise control of vasomotor and sudomotor thermal responses. Research previously reported a prolonged (~60 min) and stable elevation in esophageal temperature (T_{es}) in resting humans following exercise (Kenny et al., 1996a; Kenny et al., 2000b; Thoden et al., 1994). More recently, studies have examined the effect of exercise on vasomotor and sudomotor thermoregulatory response thresholds. These studies have indicated a ~0.4°C increase in the post-exercise esophageal temperature threshold for cutaneous vasodilation (Th_{VD}) and sweating (Th_{SW}) (Kenny et al., 1997a; 1997b; 2000b).

This link between sudomotor and vasomotor activity has been observed previously during exercise (Fox and Edholm, 1963; Fox and Hilton, 1958). However, more recent research has shown differences in the onset and pattern of sweating and active vasodilator responses during exercise. This supports the hypothesis that active vasodilatory and sudomotor activity are governed by separate neural controls (Johnson and Park, 1981; Kellogg et al., 1991b). It has been proposed that non-thermoregulatory reflexes (i.e., baroreceptor activity) modulate heat loss responses by separately modifying vasomotor and sudomotor control (Kellogg et al., 1990; Johnson, 1986). Recent evidence reinforcing baroreflex modulation shows that baroreceptor unloading similarly attenuated both warm thermal response thresholds during exercise (Mack et al., 2001).

The mechanism responsible for increasing the post-exercise esophageal temperature at which skin vasodilation and sweating begin (i.e., thresholds for vasodilation and sweating) remains unresolved. Post-exercise hypotension (i.e., decrease in arterial blood pressure) however has been associated with acute bouts of exercise (Coats et al., 1989). More recently, we have observed that the increase in post-exercise hypotension is related to an increase in exercise intensity and is paralleled by an increase in the magnitude of the post-exercise elevation in resting T_{es} (Kenny and Neidre, 2002). The post-exercise elevation in resting T_{es} seems also to be linked over a wide range of exercise intensities (40-75%VO_2max) to the exercising threshold for vasodilation (Kenny et al., 1997c). Recently, post-exercise manipulation of venous pooling by means of head down tilt and lower body positive pressure (LBPP) indicates that baroreceptor loading significantly decreases the post-exercise Th_{VD} (Kenny et al., 2000a; Jackson et al., 2000) while only slightly decreasing the Th_{sw} (Jackson et al., 2000). Thus, it would seem that exercise has a residual effect on post-exercise temperature regulation, and that modification of venous pooling by reversing the effect of baroreceptor unloading decreases post-exercise hypotension and lowers the resting Th_{VD}.

As with post-exercise skin blood flow (SkBF), reflex control of cutaneous circulation during exercise is mediated by both sympathetic active vasoconstrictor and sympathetic active vasodilator systems (Fox and Edholm, 1963; Johnson, 1986; Kellogg et al., 1989). When exercise is initiated, the reduction of SkBF in inactive regions provides additional blood flow to active skeletal muscle subsequent to metabolic demand. This reduction is accomplished solely by the active vasoconstrictor system, regardless of the thermoregulatory condition (Kellogg et al., 1991a). As steady-state exercise is continued, a rise in core temperature stimulates reflex cutaneous vasodilation and

sweating (Kenney and Johnson, 1992; Johnson et al., 1986). Other studies have shown that an attenuation of cutaneous vascular response occurs at high relative exercise intensities (Smolander et al., 1991; Taylor et al., 1988). The critical exercise intensity at which the threshold for cutaneous vasodilation is altered seems to be near 80% VO_2max (Smolander et al., 1991). Previous research has indicated that non-thermoregulatory baroreceptor reflex activity stimulates vasoconstriction, thus preventing reductions in cardiac filling and reducing thermoregulatory vasodilation (Kenney and Johnson, 1992). Thus, the elevated Th_{VD} associated with increasing exercise intensity (Johnson and Park, 1981; Kellogg et al., 1991b) is thought to be caused by a delay in the activation of the vasodilator system (Kellogg et al., 1991b). This reflex adjustment favouring muscle perfusion over thermal reflexes delays the blood flow demand from cutaneous circulation. In contrast, the exercising threshold for sweating does not appear to be influenced by exercise intensity (Kondo et al., 1998; Taylor et al., 1988).

There is little information that may explain the post-exercise elevation in the threshold for active vasodilation and sweating following relatively high exercise intensities. Thus, the purpose of this study was to examine the effect of exercise intensity on the sensitivity of post-exercise local response and central control for vasomotor and sudomotor activity. Specifically, this study included an evaluation of the control mechanism(s) for cutaneous vasomotor control through the examination of the role of vasoconstriction and active vasodilation on the post-exercise warm thermal responses.

1.1 Rationale

Previous studies have demonstrated a prolonged and stable elevation in resting esophageal temperature following dynamic exercise (Kenny et al., 1996a; 2000b; Thoden

et al., 1994). Further studies have shown an increase in the post-exercise Th_{VD} following repeated cycles of exercise and recovery increasing pre-exercise T_{es} (Kenny et al., 1996b). Recently, a wide range of exercise intensities (40-75%VO_2max) have indicated elevations in post-exercise resting T_{es} corresponding to the exercising threshold for vasodilation (Kenny and Neidre, 2002). Exercise studies have shown that SkBF and Th_{VD} are unaffected at intensities ranging from 50 to 80 %VO_2max. However, beyond a certain intensity (80% VO_2max) the vasodilation response threshold seems to be significantly attenuated (Smolander et al., 1991; Taylor et al., 1988).

It was unclear if an increase in exercise intensity would result in a similar post-exercise attenuation in skin blood flow. Therefore, we studied 1) the mechanism responsible for the post-exercise elevation in Th_{VD} and; 2) the control of post-exercise sudomotor and vasomotor activity in order to determine if they were subject to the same thermal and non-thermal reflex controls as during exercise. Simply stated, does increasing exercise intensity result in parallel increases in post-exercise Th_{VD} and Th_{SW}?

1.2 Hypothesis

Based on the results of the work of Taylor et al. (1988) and Smolander et al. (1991) that indicated a significant attenuation in the SkBF response at high relative exercise intensities, and the work of Kenny et al. (1996; 1997a; 1997b; 2000b) showing post-exercise elevation in resting T_{es} and Th_{VD}, it was hypothesised that high exercise intensity (>80VO_2max) would result in an attenuation in the post-exercise threshold for active vasodilation and sweating. Further, based on the results of Kellogg et al. (1993), it was hypothesised that a delay in the activation of cutaneous vasodilation would be the mechanism responsible for this attenuation.

1.3 Statement of the problem

In an effort to investigate the mechanism(s) responsible for the elevation of post-exercise Th_{VD} and Th_{SW}, and by means of measuring the time course changes of esophageal and skin temperature, skin blood flow, sweat rate, arterial pressure and heart rate, this study examined the effect of light (55% VO_2max), moderate (70% VO_2max) and intense (85% VO_2max) exercise on the post-exercise core temperature threshold for both warm thermal responses.

1.4 Objectives

The objectives of the study were to:

- Investigate the post-exercise esophageal temperature threshold for cutaneous vasodilation at different exercise intensities by whole body warming under selective, local sympathetic vasoconstriction bretylium blockade;
- Investigate the post-exercise esophageal temperature threshold response for sweating by whole body warming following different exercise intensities.

1.5 Relevance

This study is relevant to two distinct domains. First, form the point of view of basic research the study will contribute to the knowledge of thermoregulation in general, and specifically, to post-exercise temperature regulation. At the same time, valuable insight will be gained into the mechanism(s) responsible for post-exercise elevation in the thresholds for active vasodilation and sweating. Secondly, from a practical point of view, this study will help to elucidate the factors causing heat injury. Specifically, those injuries

resulting from heat load during exercise of high intensity, and those heat dissipation injuries related to post-exercise increases in heat loss response thresholds.

1.6 Delimitations

The interpretation of the results is limited to those included in the population studied. That is to male and female university students who are active and training on a regular basis. As well, the interpretation of the results will be limited to the population of women studied because of the hormonal changes that take place during the menstrual cycle, causing changes to core temperature.

1.7 Limitations

The present study required subjects to exercise at light (55%VO_2max), moderate (70%VO_2max), and intense (85%VO_2max) exercise levels for a moderate period of time (15 min) while monitoring surface and core temperatures. Skin blood flow was also measured using a laser-Doppler flowmeter taped to the forearm. Bretylium tosylate was delivered by means of iontophoresis to block local vasoconstriction of the skin. In addition, blood pressure and core temperature at the esophageal site were constantly monitored. The subject participatory rate could have been negatively affected by these procedures, which may have reduced the experimental group.

1.8 Definitions

Baroreceptors : Sensory nerve terminals located in the carotid sinuses and in the aortic arch that respond to changes blood in pressure. Also called pressoreceptors.

Bretylium tosylate : Bretylium is a positively charged, anti-adrenergic drug agent that is taken up by the adrenergic neurons. It blocks the release of norepinephrine within the nerve terminal without interfering with axon transmission.

Core temperature : It is described as the integration of temperatures monitored throughout the body and integrated at the hypothalamus. For the purpose of this study, core temperature represents the temperature measured at the esophageal site very close to the right atria and the ascending aorta at the level of the heart.

Iontophoresis : Is the introduction of ions of soluble salts into the tissues of the body by means of current as a result of an applied electric field.

Sweating threshold : Is the onset of sweating; resulting from an elevation in core temperature from pre-exercising 'set-point' or 'neutral zone' levels. Specifically, in this study it is expressed as esophageal temperature very close to the right atria and the ascending aorta.

Thermoregulation : Is defined as the regulation of body temperature accomplished by a complex set of responses involving the autonomic, somatic, and hormonal systems; the main control centre is found within the hypothalamus.

Vasoconstriction : Is defined as the narrowing of the lumen of blood vessels (especially of arterioles) leading to decreased blood flow to the area of vasoconstriction.

Vasodilation : Is defined as the active or passive widening of the lumen of blood vessels (especially the lumen of arterioles) leading to increased blood flow to the area of vasodilation.

Vasodilation threshold : Is the onset of active skin vessel dilation; resulting from an elevation in core temperature from pre-exercising 'set-point' or 'neutral zone' levels.

Specifically, in this study it is expressed as esophageal temperature very close to the right atria and the ascending aorta.

CHAPTER II

2.0 Review of Literature

2.1 Introduction

The aim of the present study was to investigate the effect of exercise intensity on the control of the post-exercise esophageal temperature threshold for cutaneous vasodilation through the use of selective abolition of vasoconstrictor tone by local iontophoresis of bretylium tosylate. Accordingly, the following review will address the historical and current research literature on human thermoregulation. Particularly, it will develop a framework for understanding thermoregulatory and non-thermoregulatory mechanisms involved in temperature regulation at rest, during and, post-exercise.

2.2 Basic human thermoregulation

In the human body, temperature is regulated about a mean value of 37°C ± 0.6°C (Hammel et al., 1963; Schafer, 1992). This equilibrium is maintained by the constant adjustment of the body's thermogenic and theromolytic mechanisms. Fluctuations in internal temperature occur naturally as a result of sleeping patterns, food intake, physical work, arousal, stress and even the earth's rotation (Hensel, 1973; Schafer, 1992). In women, temperature increases as high as 1°C are common during the luteal phase of the menstrual cycle (Frascarolo et al., 1992; Hessemer and Bruck, 1985; Pokora and Grucza, 2000). Other factors such as hydration state, exercise and fever affect the temperature of

the body. The following section will examine the most common theories and concepts that govern thermoregulation.

2.2.1 Set Point theory

Many models of thermoregulation in man have been proposed to describe the physiological processes involved in homeotherms (Stolwijk and Hardy, 1966). However, the classic 'set point' theory based on temperature regulation, modulated by a feedback system seems to be one of the most widely accepted (Gisolfi and Wenger, 1984; Hammel et al., 1962; Hensel, 1973; Schafer, 1992; Johnson and Ruhling, 1985; Tam et al., 1978).

Hardy (1953) was among the first to treat the thermoregulatory system as a controller operating against a set point. The theory is based on a negative feedback mechanism that regulates net heat loss from the body and the rate of heat production by the metabolism. This feedback loop is activated by thermoreceptors located both at the periphery and in the central nervous system. Temperature input signals have also been found to arise from several different structures including: a) the preoptic area of the anterior-hypothalamus, b) posterior hypothalamus, c) mid-brain, medulla, motor cortex and thalamus, d) spinal cord, f) skin, and g) viscera. Afferent signals originating from receptor activity are sent to the preoptic area of the hypothalamus where they are juxtaposed to a reference temperature referred to as the set point. The difference between the input and set point represents the load error which will determine the type and magnitude of the effector response (Gisolfi and Wenger, 1984). If the load error is positive (i.e., core temperature (T_c) measured by arterial blood greater than the set point), then the effector response will elicit a heat loss response (i.e., vasodilation and sweating) the magnitude of which depends on the load error (Johnson and Ruhling, 1985). On the

other hand, if the load error renders a negative value, vasoconstriction and shivering occur in varying degrees to minimize heat loss and increase body heat production.

Body temperature changes as a result of modifications of heat absorption from endogenous sources (metabolism) or from exogenous sources in the external environment. Changes in the quality of the external environment are sensed and mediated by cutaneous thermoreceptors directly linked to the central nervous system. Internal thermal disturbances are mediated by blood flow to the hypothalamus whose temperature acts as the set point. Thus as reported by Hardy (1973), the posterior hypothalamus is the area in which the integration of afferent signals is completed and the central efferent signals developed.

Illustrated in figure 1 are the basic elements of a human thermoregulatory control system. In this model, body temperature is the controlled system. Disturbances of the controlled system arise from endogenous and exogenous stresses. These disturbances create changes that are detected by sensors which in turn generate a feedback signal. Any deviation of the controlled variable from the reference signal produces a load error that activates the controller (Hensel, 1973). The error signal serves as the command signal to the controller, which initiates a control action to offset the deviation of the controlled variable. The temperature-independent reference signal, against which the feedback signal is compared, is termed the set point of the system.

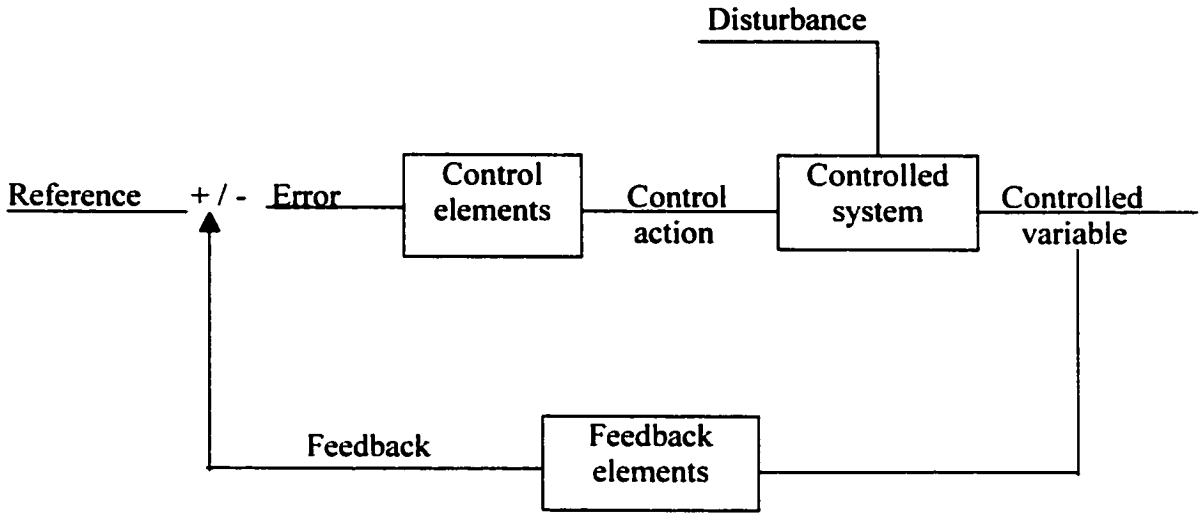

Figure 1. Closed loop negative-feedback control system (From Hensel, 1973)

In a 1963 study, Hammel et al. examined the set point theory by investigating the role of hypothalamic and skin temperature in the control of thermal response in animals (i.e., dog and monkey). They suggested that the set point could be artificially manipulated by lowering or increasing skin and extra-hypothalamic temperature by surrounding the hypothalamus with water perfused thermodes.

In a later study, Hensel (1973) defined the set point as that value of the controlled variable at which the control action is zero. Thus, a point where no thermoregulatory efferent signals are developed. Furthermore, it was suggested that the set point or onset threshold of various effector responses, such as shivering or panting are not identical. Therefore, the whole body set point temperature must be viewed as a function of various onset thresholds for metabolism, evaporation, vasomotor and sudomotor adjustments. Using this same definition, Tam et al. (1978) studied core temperature and sweating responses at rest and during exercise while maintaining constant skin temperature (T_{sk}) at various temperatures between 20 and 35°C. Results from this study revealed that the

threshold for sweating was influenced by venous temperature and that the effect of exercise was to lower the gain of the sweating response. These findings support earlier results of exercising dogs encountering an increase in evaporative heat loss at lower hypothalamic temperatures compared to resting dogs (Jackson and Hammel; 1963).

Following these early investigations, Gisolfi and Wenger (1984) defined the set point as purely a mathematical concept that is useful for describing the thermal control of effector responses. The concept does not imply a particular neural model of thermoregulation or set temperature, but describes different recruitment stages within the magnitude of the load error. In effect, at any moment there is only one load error characterizing the thermal state of the organism. However, each effector response (onset threshold) is characterized by a different recruitment stage for initiating heat dissipating responses within the load error (e.g., onset threshold of sweating before that of vasodilation within the load error). In addition, any perturbation of the central thermoregulatory controller displacing the set point will result in a shift of all effector thresholds in the same direction (Gisolfi and Wenger, 1984). Finally, endogenous pyrogens resulting in fever seem to be the only perturbation causing a shift in set point (Gisolfi and Wenger, 1984; Johnson and Ruhling, 1985).

In summary, any deviation from the hypothalamic temperature set point leads to various control actions (changes in heat production, thermal insulation, and evaporative heat loss) that tend to reduce the deviation of temperature (Hensel, 1973).

2.2.2 Null Zone theory

Contrary to the concept of set point, the 'null zone' theory describes a body temperature thermo-neutral zone delimited by thermogenesis and thermolysis on

respective sides being proportionally mediated by environmental stresses (Hardy et Dubois, 1938). Thus, core temperature is situated between two critical temperatures whose range is defined as the ambient temperature within which metabolic rate is at a minimum, and within which temperature regulation is achieved by non-evaporative physical processes alone (Bligh and Johnson, 1973).

Cabanac and Massonnet (1977) investigated the core null zone in humans by observing sweating and shivering responses as well as changes in vasomotor tone. In the following study, core temperature at the esophageal site was monitored in resting subjects who were sequentially immersed in baths of 38°C and 28°C in order to isolate sweating and shivering thresholds respectively. Results indicated no null zone between the esophageal temperature threshold for shivering and the onset threshold for vasodilation and sweating. This led them to conclude that there is no null zone of core temperature but that responses are either of the hyperthermic or hypothermic type, without a euthermic type. Thus, the human organism is in constant or virtual thermoneutrality permanently being equilibrated between hyperthermia and hypothermia.

In a similar study investigating the influence of non-thermal factors on thermoregulatory effector thresholds, Mekjavić and Bligh (1989) induced sweating by raising body temperature either by water immersion (38°C) or by exercise on a cycle ergometer in air (~20°C). As with the previous study, subjects were immersed in a 28°C bath following exercise where they rested in order to monitor the cold response threshold. The results indicate that the rate of decrease of esophageal temperature was three times greater after passive heating (water immersion) compared to active heating (exercise in air). These findings are associated with skin temperature changes occurring during the cooling phase of the 38°C water immersion trial. The transfer from warm water to the

28°C cooling bath resulted in cooled venous blood returning to the heart form the periphery causing a rapid decrease in esophageal temperature, which was not observed after exercise in air at ~20°C. Furthermore, shivering thermogenesis was not provoked even though esophageal temperature fell sufficiently below sweating cessation, indicating a thermoregulatory null zone between the extinction of sweating and the core temperature threshold for shivering.

In a subsequent study by Mekjavić et al. (1991) the hypothesis that the core temperature thresholds for sweating and shivering do not coincide and are separated by a null zone was examined. They refer to the null zone as a zone in which thermoregulatory processes are inactive or as a zone bound by the threshold for cessation of sweating at the upper limit and onset of shivering at the lower limit. Using an adapted version of the previous designs, they instructed subjects to exercise on an immersed (28°C) cycle ergometer at 50% of their maximum work rate for 20 min. Recovery observations were monitored for 100 minutes in the immersion bath and revealed a significant difference between the core temperature at which sweating ceases and shivering commences regardless of the site of core temperature measurement (i.e., rectal, esophageal). Thus, results confirm the existence of a thermoregulatory null zone between the shivering thermogenesis threshold and that of sweating.

Finally, the human thermoregulatory control system appears to defend core temperature within a zone of thermoneutrality, which is defined by a range of peripheral temperatures that do not elicit thermoregulatory effector responses when deviations in internal temperature remain within this zone (Bligh, 1988; Mekjavić et al., 1991).

2.3 Temperature regulation and environmental interaction

The human body has three physical mechanisms that govern heat exchanges with the environment which can be divided into sensible (dry) and insensible (evaporative) heat transfers. Conduction and radiation, both sensible, along with evaporation act primarily across the skin to dissipate heat and maintain homeothermia (Schafer, 1992). The rate of heat exchange is modified externally and internally through changes in ratio of fluid (i.e., blood, water, air) currents over the relatively hotter or cooler tissues. Thus, dissipation by conduction of heat from hotter tissues (such as muscle) is accelerated by changes in blood flow. Changes in blood flow to the skin and peripheral tissues, accelerate the rate of conduction loss in the skin. At the skin interface with air, conductive and evaporative rates are modified by changes in airflow. The body's heat content is the primary factor influencing thermal equilibrium. Therefore heat storage (S) is influenced by metabolic heat production (M), conductive heat loss or gain (C), radiative heat loss or gain (R) and evaporative heat loss (E):

$$S = M \pm C \pm R - E$$

Heat transfers via conduction are direct exchanges between molecules in contact where kinetic energy is transferred between matter (Schafer, 1992). For example, heat produced internally by working muscles can be transferred adjacently to other tissues through conductive blood flow ultimately reaching the skin and periphery to be dissipated (negative heat transfer). Conversely, a positive heat transfer occurs when the surrounding environment is warmer than the skin, thus creating conduction to the skin. The rate of conduction is proportional to the temperature gradient between the skin molecules and those surrounding the body. Furthermore, conduction can occur through air, water and articles of clothing.

In normal ambient temperature (21 to 25°C), resting humans lose heat in excess of 60% from radiation. This concept is associated with the fact that all surfaces above absolute zero radiate energy in the form of electromagnetic radiation, and the rate of radiation is proportional to the fourth power of the temperature of the radiating surface (Schafer, 1992). Radiation is thus a heat transfer mechanism where radiant energy flows between relatively hot bodies and where net exchanges depend on the temperature gradient between objects from hotter to cooler bodies (Morehouse and Miller, 1971). Accordingly, a net heat transfer (net heat loss) from the body to the environment occurs when the temperature gradient between the skin and air is positive (i.e., skin temperature is higher than air temperature) and a net heat gain is seen when T_{sk} is cooler than the air.

Moreover, energy is required to convert liquid water to a vapor. This energy is referred to as latent heat of vaporization, and is equal to 580kcal/L of water vaporized (Schafer, 1992). Hence, the rate of heat lost from the body through evaporative pathways in kilocalories per hour ($J_{Q,evap}$) is directly proportional to the rate at which water evaporates from the skin surface and the respiratory passages (J_{H2O}) in liters per hour:

$$J_{Q,evap} = -(580\text{kcal/hr}) \cdot J_{H2O}$$

In humans at rest, evaporative heat losses account for approximately 20 to 25 % of the total heat loss. These losses are relatively constant and prevent the body from facing a gain in endogenous heat. Heat loss through evaporation occurs through two channels of insensible heat dissipation, consisting of loses through the skin (i.e., perspiration) and lung surfaces (i.e., respiration) (Fortney and Vroman, 1985). Under sedentary conditions, the basal rate of insensible water loss is about 500 ml/day including losses from the skin and ventilation, resulting in a loss of approximately 300 kcal per day. However, during exercise in thermal neutral environments, evaporation is the primary heat loss mechanism

proportionately increasing respiratory evaporation up to 10-fold in relation to metabolic rate. In spite of this, in the overall heat balance during exercise, the contribution of respiratory water loss is nearly negligible when compared to sweating and sensible perspiration water losses (Fortey and Vroman, 1985). The rate of heat loss by evaporation is dependent on the water pressure (P_{H2O}) gradient between the skin surface and the air and accounts for 80% of total losses during exercise while conduction and radiation account for a maximum of 20%. Even at low ambient temperature, water is constantly being lost from the body by evaporation. During exercise, the internal heat rise produces an increase in perspiration generating added sweat (water) which is evaporated, thus causing the evaporation response to become an active (sensible) process. Sweat evaporates by absorbing cutaneous heat and is transformed to a gaseous state. However, for heat loss to occur by sweating there must be a water vapour gradient between the skin and the air. Thus, evaporative heat loss is extremely dependent on relative humidity of the air. When air surrounding the skin is saturated with water, no heat can be lost to the environment. Consequently, evaporation is much less effective in humid conditions.

The rate of heat exchange with the environment by conduction and evaporation depend largely on the movement of air or water surrounding the skin, which is referred to as convection. When skin is surrounded by motionless air or water, molecules form an insulating layer around the body acting like a second skin, thus minimizing the effects of conduction and heat loss (Vander et al., 1985). As an example, since it is a gas and relatively good insulator with low thermal conductivity, air must be moved by bulk movements or a breeze to allow a reduction in the surrounding insulation layer, resulting in a greatly enhanced heat exchange by conduction. This effect of convection increases geometrically (Eq. 2) with an increase in wind velocity and is called forced convection

(Schafer, 1992). Together in thermal neutral conditions, convection and conduction account for 15 to 20% of heat loss to the environment. Conversely, air cannot absorb energy in the infra-red zone. Thus, convection has no effect on radiation heat loss because this exchange mechanism involves only the temperature differences between the skin and actual objects in the environment. However, convection does increase evaporative heat loss from the skin. When the air adjacent to the skin is still, it becomes saturated with water resulting in a decreased evaporation. Thus, by supplying fresh air with a lesser water content (i.e., decreased saturation), evaporation is enhanced because of the lowered P_{H2O}.

Clearly, these temperature regulating environmental interactions occur naturally. The body reacts appropriately to the environment and regulates the appropriate processes to maintain relative constant temperature. This equilibrium is maintained by balancing metabolic rate (M) and thermolysis by evaporation (E), and mechanical work (W) by radiation (R) and by conduction (C):

$$M = E \pm (R + C) \pm W$$

2.4 Thermoregulatory control of cutaneous circulation at rest

Over a certain range of conditions, resting humans regulate body (core) temperature without shivering or sweating (Dubois, 1939; Hardy, 1961). Within this range, adjustments in the regulation of skin blood flow, control thermal balance (Savage and Brengelmann, 1996). This null zone or neutral zone of temperature regulation is better defined in terms of skin temperature, which is the outcome of the thermal interaction among the environment, clothing, and body heat production. The reflex influence of skin temperature on SkBF dominates within the 33-35°C range of skin

temperature to maintain thermal balance (Savage and Brengelmann, 1996). Thus, the reflex adjustment of skin blood flow responding to a change in skin temperature results in a slight overcompensation in thermal balance by moving core temperature in the opposite direction. Consequently, an equilibrium core temperature is established when the resultant feedback influence of core temperature on SkBF corrects the thermal imbalance (Savage and Brengelmann, 1996). Furthermore, under thermal neutral conditions, the skin receives ~ 5 to 10% of cardiac output, whereas under conditions of heat stress, skin blood flow can reach 50-70% of cardiac output, approaching 8 l/min (Johnson and Proppe, 1996; Rowell, 1977). In these situations, warm blood is redistributed from the core to the skin so that through radiation, conduction and evaporation heat is lost to the ambient surroundings at a rate proportional to the difference between skin and ambient temperature (Fortney, 1985).

2.4.1 Control mechanisms for vasodilation and vasoconstriction at rest

Cutaneous vasomotor control is defined by two systems: a sympathetic active vasodilator system and a sympathetic noradrenergic vasoconstrictor system (Kellogg et al., 1989; Thomas et al., 1999). When a normothermic human is exposed to cold, reductions in SkBF associated with a reduced T_{sk} tend to conserve body heat by constricting cutaneous vessels. The reduction in SkBF is attributed to a reduction in cutaneous vascular conductance (CVC) due to the increased activity in sympathetic adrenergic vasoconstrictor nerves (Johnson, 1986; Johnson et al., 1986; Rowell, 1977). Conversely, the reflex effect of moderate increases in T_{sk} on SkBF during rest is small and has been attributed to reduced vasoconstrictor activity and passive vasodilation (Kellogg et al., 1989; Pérgola et al., 1994; Wyss et al., 1974). This indicates that the

vasoconstrictor system is able to mediate rapid changes in SkBF that are of relatively small magnitude. When heat stress is induced, internal temperature reaches a threshold beyond which the rise in skin blood flow per degree Kelvin is fairly steep, increasing active vasodilation and CVC markedly (Johnson, 1986, Kellogg et al., 1989). Although individual thresholds and slopes for the internal temperature-SkBF relationship may vary. Johnson (1986) reported an average around 37°C and 20ml·100ml^{-1}·min^{-1}·°C^{-1}, respectively.

2.4.2 Influences of local temperature on cutaneous circulation

Skin surface can be divided into two distinct regions: 1) acral regions which are innervated solely through noradrenergic sympathetic nerves, and which include the palms of the hands, soles of the feet, nose, lips and ears, and 2) non-acral regions (head, limbs and trunk) where both the vasodilator system and the adrenergic vasoconstrictor system are active (Johnson, 1986; Rowell, 1977). Cutaneous circulation in all of these regions is modulated by local factors (i.e., local temperature, pressure) and reflexes (i.e., reflexes subserving thermoregulation, pressure regulation and exercise).

Under resting conditions when initial skin temperature levels are below 34°C, the response of skin blood flow to an elevation in skin temperature is small (Pérgola et al., 1994; Wyss et al., 1974; 1975). This reflex role for T_{sk} sets the threshold for the internal temperature at which cutaneous vasodilation and/or sweating are initiated (Johnson, 1986). Thus, the response in skin blood flow to an elevation in skin temperature depends on the level of internal temperature (Johnson and Park, 1979). Reaction of low internal temperature (<36.8°C) to a rapid rise in T_{sk} would only cause a minor elevation in SkBF.

whereas an elevated T_c (>37°C) would render a noticeable increase in SkBF (Johnson, 1986).

When studied as a measure of thermal comfort, skin temperature contributed more towards subjective thermal comfort than to automatic thermoregulatory responses (Frank et al., 1999). Elevated local temperature (T_{loc}) as examined in a previous study by Taylor et al. (1984a) revealed that local warming of the skin to 42°C rendered the forearm cutaneous vasculature unresponsive to the reflex drive for vasodilation by whole body heating. Additionally, they concluded that T_{loc} of 42°C is sufficient in yielding maximal SkBF caused by a reduction or abolition of cutaneous vascular smooth muscle tone.

Modifications in local skin temperature regulate cutaneous blood vessel function by actively modulating the adrenergic neuroeffector interaction (Johnson et al., 1986). Thus, stimulation of the adrenergic nerves by local warming decreases the contractile responses of cutaneous veins (Cooke et al., 1984; Vanhoutte and Lorenz, 1970) whereas local cooling has the opposite effect (Janssens et al., 1978). Norepinephrine (NE) response to temperature changes reflect modifications in the affinity of postjunctional α-adrenoreceptors on the venous smooth muscle (Janssens et al., 1978). Cutaneous veins and thermoregulatory blood vessels are distinctive amid vascular smooth muscle containing both α_1-adrenergic and α-$_2$-adrenergic post-junctional receptors (DeMey and Vanhoutte, 1981; Flavahan et al., 1984). Studies selectively manipulating α-adrenergic agonists and antagonists have established the α_2-adrenergic component of the response to norepinephrine to be modulated by cooling and warming (Cooke et al., 1984). Pérgola et al. (1993) went on the show that in humans: 1) intact adrenergic nerve terminals and NE release, but not sympathetic activity per se, are required for the immediate vasoconstrictor

response to local cooling; 2) the stimulus for the release of the NE is local, possibly by axon reflex; 3) responses to prolonged local cooling involve mostly noradrenergic mechanisms; and 4) the majority of the vasodilator response to local warming does not require an intact adrenergic system.

As demonstrated, both the sympathetic active vasodilator and the sympathetic noradrenergic vasoconstrictor systems influence cutaneous vascular response.

2.5 Thermoregulatory control of cutaneous circulation during exercise

Exercise performed adiabatically (i.e., without heat loss to the environment) would continuously raise T_c in linear fashion throughout the exercise bout making it impossible to withstand even short exercise periods (Kenney and Johnson, 1992). However, humans can tolerate internal temperatures below 35°C or above 41°C only for brief amounts of time, and living cells have a maximal tolerance limit range from 0°C (ice crystal formation) to about 45°C (thermal denaturation of intracellular proteins) (Kenney, 1998). Fortunately, the human body has developed highly specialized physiological mechanisms that respond to acute thermal stresses such as exercise. Intended to dissipate, conserve or produce body heat, these responses involve the coordination and/or competition of distinct thermal mechanisms.

2.5.1 Exercise initiation and cutaneous circulation

Core temperature is monitored by a central controller receiving sensory information via nerves stemming from deep body and peripheral thermoreceptors (Gleeson, 1998). Peripheral (skin) thermoreceptors deliver input regarding ambient/environmental thermal conditions. Whereas, blood flow to the brain

representative of internal temperature is monitored by central thermoreceptors located in the hypothalamus. Input from the latter of these receptors predominates effector response in order to prevent a rise in thermal load.

When dynamic exercise is initiated, vasomotor reflexes redistribute blood flow from inactive tissues to working muscles (Buskirk, 1977; Kenney and Johnson, 1992; Johnson and Park, 1982). Benedict and Parmenter (1929) were the first to note a fall in hand skin temperature with exercise, indicating a cutaneous vasoconstrictor response. Likewise, through the separation of skin and muscle components with iontophoresis of epinephrine, Zelis et al. (1969) demonstrated a cutaneous vasoconstriction of the forearm with initiation of leg exercise. Furthermore, venous occulasion by pletysmography measurements have confirmed a pronounced vasoconstriction with the onset of dynamic leg and upright exercise (Hirata et al., 1983; Johnson et al., 1974). Vascular constriction in the skin at the beginning of exercise has also been demonstrated by combining laser-Doppler flowmetry and iontophoresis of bretylium tosylate to measure perfusion of skin vessels without the influence of underlying muscle tissue (Kellogg et al., 1989; 1993).

Clearly, vasoconstriction has a reflex effect at the onset of exercise in normothermic settings. Even in hyperthermic conditions, cutaneous vasoconstriction is detectable at exercise initiation. The warmer environment causes a reflex increase in cutaneous circulation generating a greater reduction in SkBF when exercise is begun, overriding hyperthermia (Johnson and Park, 1982). Local heating as presented parallel findings when pre-exercise SkBF values are raised. Taylor et al. (1984a) observed responses in forearm blood flow for different local temperatures during leg exercise. Results indicated a vasoconstriction with the onset of exercise for all pre-exercise local temperatures except 42°C, indicating that at 40-42°C the cutaneous vasoconstrictor

response to exercise initiation is attenuated. Thus neurologically mediated vasoconstrictor responses are effectively blocked by disturbance of sympathetic function or blood vessel responsiveness caused by local heating above 40°C (Johnson et al., 1986).

2.5.2 Prolonged exercise and cutaneous circulation

As exercise continues, T_c rises in response to metabolic heat production evoking cutaneous vasodilation and sweating (Kenney and Johnson, 1992; Johnson et al., 1986). Although there is competition from vasoconstrictor reflexes, Johnson (1986) reported a net cutaneous vasodilation that depends in part on thermal conditions (both internal and ambient). Brengelmann et al. (1977) and Nadel et al. (1979) showed that SkBF rises with internal temperature in warm settings, but that in the upright position the increase is attenuated as T_c reaches 38°C. In an investigation blocking the vasoconstrictor system with iontophoresis of bretylium, Kellogg et al. (1993) failed to abolish the attenuation phase of the CVC-T_{es} relationship. Thus, they demonstrated that vasoconstrictor activity was not responsible for the levelling off of SkBF, but that an upper limit to active vasodilator tone was the cause. In addition, the untreated sites with a functional vasoconstricor system were reported to have a less pronounced attenuation phase, indicating slow withdrawal of vasoconstrictor tone. Furthermore, when local heating was applied, SkBF and consequently CVC rose above exercise values indicating the attenuation phase was not the result of maximal cutaneous vasodilation (Kellogg et al., 1993; Taylor et al., 1984b). In light of these results Kellogg et al. (1993) concluded that the attenuated rate of rise in SkBF during this phase is due to a limitation in active vasodilator activity. This limitation to vasodilation while exercising may be the result of baroreceptor reflexes (sinoaortic and/or cardiopulmonary) which would limit or reduce

SkBF in response to increases in cutaneous venous volume (Brengelmann et al., 1977; Johnson, 1986; Mack et al., 1988). In effect, blood pressure regulation would be challenged by increases in cutaneous vascular conductance through an increase in cardiac output and peripheral blood distribution, and respond by reducing SkBF through baroreceptor reflexes.

2.5.3 Influence of exercise intensity on cutaneous circulation

Exercise influences vasodilator activity by raising the internal temperature thresholds relative to rest (Johnson and Park, 1981; Kellogg et al., 1991a). Interestingly, the increased threshold is entirely caused by a delay in the activation of the vasodilator system, with the vasoconstrictor system having no involvement (Kellogg et al., 1991b). As internal heat production raises T_c beyond the threshold, vasodilation is utilized to dissipate heat to the environment in order to match metabolic production. Within 10-15 min depending on exercise intensity, a steady state T_c is attained (Kenney and Johnson, 1992). However as exercise intensity increases in warm environments, reductions in cardiac filling may stimulate baroreceptor modulated vasoconstrictor reflexes causing a reduction in performance or even hyperthermia. Normally, submaximal efforts performed during prolonged exposure to high ambient temperature conditions provoke such outcomes (Fortney and Vroman, 1985). Maximal exercise performance is generally not altered in warm environments unless initial T_c is elevated. Nevertheless, exercise intensity does produce alterations in thermoregulatory responses caused by absolute metabolic intensity (VO_2) rather than size of muscle mass employed (Sawka et al., 1984).

In 1983, using a gradient layer type direct calorimeter, Hirata et al. measured nonevaporative (radiation and convection) and evaporative (evaporation) heat loss. Their

results indicated a reduction in thermoregulatory vasodilation caused by increasing vasoconstrictor tone as a non-thermal factor responding to increasing exercise intensity. Similarly, attenuations were reported by Smolander et al. (1987) when they examined forearm blood flow responses to incremental exercise in ambient temperatures of 25 and 40°C. They showed that forearm blood flow (FBF) increased linearly with the rise in T_c above the threshold for vasodilation. However, at the highest workload of ~150W, FBF responses in relation to T_{es} were significantly attenuated for both environmental conditions. A subsequent study using five different exercise intensities (50, 60, 70, 80 and 90% VO_2max) revealed that at the lower workloads of 50 to 70 % VO_2max, there were no significant differences in the T_{es} thresholds (37.42°C, 37.48°C and 37.59°C) or slopes for skin blood flow (Smolander et al., 1991). However, at 80% T_{es} increased relatively more above steady state, and at 90% the rise in T_{es} was steep. At this higher intensity SkBF measurements indicated a marked reduction in the SkBF-T_{es} relationship resulting from exercise related reflexes favouring muscle perfusion over thermal reflexes. Vasodilation thresholds at these higher intensities (80 and 90 % VO_2max) were 37.79°C and 38.20°C respectively. These results indicating an attenuation of forearm blood flow at high intensities are in accordance with those of Taylor et al. (1988) who noted that threshold shifts affected the SkBF response to exercise above a critical workload. More recently, Kondo et al. (1998) reported regional differences (from the torso to the limbs) in the esophageal temperature threshold for vasodilation as exercise intensity increases. Furthermore, when associated to T_{es}, the Th_{VD} was higher at 65%VO_2max (37.28°C) compared to 35 % (37.06°C) and 50 % (37.11°C).

Exercise intensity is but one factor influencing the regulation of body temperature. Physical training has been shown to reduce physical strain and heart rate while improving exercise-heat tolerance and increasing sweat rate (Armstrong and Maresh, 1998; Chueng, et al., 2000). Others factors have also been known to influence thermoregulation such as: body composition (Glickman-Weiss et al., 1999; Prisby et al., 1999; Yoshida et al., 1998), human morphology (Anderson, 1999), circadian rhythm (Chueng et al., 2000), aging (Frank et al., 2000; Kenney, 1988; Shibasaki et al., 1999; Smolander et al., 1990), gender (Bar-Or, 1998; McLellan., 1998; Tikuisis et al., 2000), hydration state (Nadel et al., 1980; Noakes, 1998), acclimation (Buskirk, 1977; Cochrane and Sleivert, 1999) exercise posture (Johnson et al.,1974; Johnson and Park 1981), and menstrual cycle (Frascarolo et al., 1992; Pokora and Grucza, 2000).

With such a host of factors influencing thermoregulatory mechanisms, the perplexity of body temperature regulation becomes increasingly interesting. The following section will address human thermoregulation, more specifically post-exercise cutaneous circulation.

2.6 Thermoregulatory control of cutaneous circulation post-exercise

As indicated by pre-exercise and exercise responses, cutaneous vasculature reacts specifically to the conditions and stimuli encountered. Post-exercise haemodynamic responses have been shown to sustain an elevated systemic vasodilation lasting over 60-min (Coats et al., 1989). This hypotensive period is associated to a reduction in systemic blood pressure resulting in an elevated heart rate and cardiac output.

2.6.1 Cutaneous circulation post-exercise

Previous research has demonstrated that subjects exercising at 75% VO_2max for 18 min maintain a stable elevation (~0.3-0.5°C) in post-exercise esophageal temperature while rectal and all remaining surface temperatures display continuous falls except for finger (Kenny et al., 1996b; 1997b; 2000b; Thoden et al., 1994). This sustained (i.e., 65 min) post-exercise increase in esophageal temperature seems to be equal in magnitude to the exercising threshold for vasodilation. Further research has indicated that 15 to 45 min of steady-state exercise does not alter the magnitude of elevation in post-exercise esophageal temperature (Kenny et al., 1997c). However, it has been demonstrated that successive 15 min bouts of exercise separated by 30 min of recovery result in a further elevation of pre-exercise resting core temperatures and ultimately the esophageal temperature threshold for vasodilation (Kenny et al., 1996b). Progressive maximal exercise does not result in a similar elevation of post-exercise esophageal temperature or threshold for vasodilation as observed in steady-state activity (Kenny et al., 2000c).

Research form the same laboratory (Kenny et al., 1996a) has also revealed that metabolic heat load (exercise) resulted in a similar esophageal temperature plateau corresponding to the exercise threshold for vasodilation. However, non-metabolic heat load (warm-water immersion) did not result in the same post-treatment esophageal temperature increase. Hypothalamic temperature modifications resulting from the exercise thermal effects of : metabolic (Johnson and Ruhling, 1985), osmolarity (Fortey and Vróman, 1985), endocrine (Horowitz, 1990), and plasma volume (Nadel et al., 1980; Nishiyasu et al., 1991) changes could lead to the recovery differences observed between metabolic and non-metabolic heat loads. Vasoconstriction and shivering are also known

to be influenced by exercise-related residual factors increasing respective response thresholds well into recovery (Kenny et al., 1998).

2.6.2 Baroreceptor influence on post-exercise cutaneous circulation

Coats et al. (1989) showed that progressive maximal exercise resulted in an elevation of systemic vasodilation for at least one hour following exercise. The observed hypotensive period indicates a non-thermal, baroreceptor influence on post-exercise temperature regulation. This observation is consistent with an elevated threshold for both warm thermal responses during recovery (Kenny et al., 1996a; 1996b; 2000b).

Post-exercise hypotension and the subsequent elevation in the esophageal temperature threshold for vasodilation seem to be observed over a wide range of exercise intensities (40-75%VO_2max) (Kenny et al., 1997c). Recently, post-exercise hypotension as been linked to an increase in resting esophageal temperature (Kenny and Neidre, 2002). Specifically, the increase in post-exercise hypotension was related to an increase in exercise intensity and paralleled by an increase in the magnitude of the post-exercise elevation in resting esophageal temperature. Seemingly, the magnitude of the post-exercise elevation in resting T_{es} is defined by the residual heat load of the previously active musculature. Therefore, in conjunction with a post-exercise decrease in heat loss response for both SkBF and sweating (Kenny et al., 2000b) and an elevated muscle heat load, there would be a time-dependent transfer of the residual heat of muscle to the core during the post-exercise resting period. Consequently, core temperature would remain elevated as long as the heat content in the muscles remained higher, and the post-exercise hypotension was not removed (Kenny and Neidre, 2002).

In order to confirm the effect of baroreceptor activity on the post-exercise warm thermal responses, manipulation of post-exercise venous pooling by means of head-down tilt was employed (Kenny et al., 2000a). Results indicated a reversal of baroreceptor unloading in the exercise recovery phase resulting in a more adequate venous return consequently reducing the esophageal temperature threshold. Most recently, manipulation of venous pooling by means of lower body positive pressure has indicated that baroreceptor loading significantly decreases the post-exercise Th_{VD} while only slightly decreasing the Th_{SW} (Jackson et al., 2000). Thus, it would seem that modification of venous pooling by reversing the effect of baroreceptor unloading decreases post-exercise hypotension and lowers the resting Th_{VD}. Investigation of the exact mechanism(s) involved in the manipulation of SkBF and esophageal temperature thresholds in the post-exercise recovery period clearly indicates a role for baroreflex modulation. Resetting of the arterial baroreflex to a lower operating point seems to be a posible explanation for the post-exercise reduction of sympathetic outlow and arterial pressure (DiCarlo and Bishop, 2001). Through this resetting, baroreceptor unloading would elicit peripheral vasoconstriction in order to maintain blood pressure. Additionally, exercise related factors such as metabolic, endocrine, cardiovascular, osmolarity and plasma volume modifications would contribute to exercise recovery.

Sudomotor control as previously been linked to vasomotor control during exercise (Fox and Edholm, 1963; Fox and Hilton, 1958). However, separate neural controls have been proposed for the onset of active vasodilation and sweating (Johnson and Park, 1981; Kellogg, 1991b). These separate control mechanisms arise from observations of differences in the onset and pattern of sweating and active vasodilator responses during exercise. Non-thermoregulatory reflexes (i.e., baroreceptor activity) tend to modulate heat

loss responses by separately modifying vasomotor and sudomotor control (Kellogg et al., 1990; Johnson, 1986). Recent evidence for baroreflex modulation has shown that baroreceptor unloading similarly attenuated both warm thermal response thresholds during exercise (Mack et al., 2001).

2.7 Baroreceptor modulation of cutaneous circulation

Sinoaortic and cardiopulmonary baroreceptors are mechanoreceptors that detect arterial pressure variations. The former are stretch receptors located in the carotid and aortic sinuses. The latter mechanoreceptors are present in the atria, ventricles, and pulmonary vessels. The primary role of baroreceptors is to mediate transitory changes in arterial pressure brought about by postural or lower body pressure modifications. For example when arterial pressure is elevated (i.e., baroreceptor loading), the receptors are stretched which sends a more frequent influx to the vasomotor center. The response is an inhibition of the vasomotor center resulting in vasodilation and reduction of arterial pressure. Conversely a reduction of mean arterial pressure (i.e., baroreceptor unloading) yields vasoconstrictor reflexes and an increase in cardiac output elevating arterial pressure.

Baroreceptor unloading initiated through simulated orthostasis (i.e., head up tilt (HUT) and lower body negative pressure (LBNP)) seems to modulate cutaneous blood flow during resting conditions (Crandall et al., 1996; Kellogg et al, 1990; Mack et al., 1988). With the use of bretylium iontophoresis and LBNP, Kellogg et al. (1990) concluded that baroreceptor unloading elicits a withdrawal of active vasodilator tone and that the baroreflex has control of the active vasodilator system. In 1995, Mack et al. investigated the interaction between baroreceptor-modulated blood pressure-regulating

reflexes and thermoregulatory control of SkBF and sweat response. Their conclusions indicate that baroreceptor unloading by LBNP: 1) limited cutaneous vasodilation during dynamic exercise by increasing the core temperature threshold for vasodilation and attenuating the rate of rise of SkBF per unit increase in core temperature; and 2) attenuated thermoregulatory control of sweating by reducing the rate of rise in local chest sweat rate per unit increase in core temperature. Mack et al. (2001) further demonstrated that during exercise, baroreceptor unloading limited cutaneous vasodilation by delaying the onset of cutaneous vasodilation and limiting peak CVC. However, this was immediately reversed after removal of the blood pressure challenge (i.e., LBNP). Research by Jackson et al. (2000) found that the post-exercise increase in the threshold for vasodilation is a result of baroreceptor unloading.

As demonstrated, baroreceptor reflexes strongly modulate post-exercise thermoregulation. As the regulation of these increases was unclear when related to exercise intensity, the use of bretylium tosylate iontophoresis isolating vasodilatory mechanisms appeared extremely beneficial. The following section will explain the principle concepts and procedures associated with iontophoresis.

2.8 Iontophoresis of bretylium tosylate

2.8.1 Laser-Doppler flowmetry and cutaneous circulation

The measurement of skin blood flow with the use of cutaneous laser-Doppler flowmetry (LDF) has been accepted and widely utilized for over a decade (Crandall et al., 1998; Kellogg et al., 1989; Mack et al., 2001; Saumet et al., 1988; Thomas et al., 1999). Laser-Doppler flowmetry or velocimetry, is based on the frequency shift of low-power

light caused by moving red blood cells in the capillaries and is used as an index of blood flow (Grossman et al., 1995; Stern et al., 1977). The measurement is specific to skin and not influenced by underlying muscle blood flow (Saumet et al., 1988). However, has previously mentioned, reflex control of cutaneous circulation involves both sympathetic vasonconstrictor and sympathetic active vasodilator systems. Although the vasonconsrictor system is known to be under noradrenergic control, the mechanism for active vasodilation is less clear (Kellogg et al., 1993).

2.8.2 Iontophoresis blockade of vasoconstriction

In 1989, Kellogg et al. explored the possibility of selectively blocking vasoconstrictor nerve activity in order to isolate and examine the control of the vasodilator system. With the combination of LDF and an established method of drug delivery, iontophoresis, they selectively blocked vasoconstrictor nerve activity with bretylium tosylate.

Bretylium tosylate was formerly used as an anti-hypertensive agent, but is now proposed as an anti-arrhythmic. It is a chemical agent that blocks the release of adrenergic transmitters. Adrenergic transmission refers to neurons that use catecholamines (a general class of ortho-dihydroxyphenylalkylamines derived from tyrosine) as neurotransmitters at a synapse when a nerve impulse passes (i.e., the sympathetic fibres). It also refers to neurones that are activated by adrenaline or substances with similar activity. Neurotransmitters are endogenous signaling molecules that alter the behaviour of neurons or effector cells. The sympathetic nervous system is one of the two divisions of the vertebrate autonomic nervous system (the other being the parasympathetic nervous system). The sympathetic preganglionic neurons have their cell bodies in the thoracic and

lumbar regions of the spinal cord and connect to the paravertebral chain of sympathetic ganglia. These innervate heart and blood vessels, sweat glands, viscera and the adrenal medulla. Most sympathetic neurons, but not all, use noradrenaline as a post-ganglionic neurotransmitter. Thus, bretylium is a positively charged, anti-adrenergic agent that is taken up by the adrenergic neurons. Once within the nerve terminal, the drug blocks the release of norepinephrine without interfering with axon transmission (Haeusler et al., 1979). The key to this approach is that the vasodilator system is unaltered while the vasoconstrictor system is inhibited by the presynaptic blockade of norepinephrine release. High levels of bretylium have toxic effects on gastrointestinal smooth muscle and cardiac muscle (Boura and Green, 1959). Therefore the use of iontophoresis, a noninvasive technique introducing ions of soluble salts into the tissues of the body by means of current (Turnell, 1921), avoids potential confounding effects of systemic drug administration and limits the possibility of overdose (Grossman et al., 1995). Moreover, the extent of drug absorption into the skin is proportional to the magnitude and duration of current applied so that the current · time product is an index of drug dose (Grossman, 1995).

2.8.3 Iontophoresis protocols

The original technique by Kellogg et al. (1989) consisted of mounting a Plexiglas chamber ($0.64cm^2$) on the ventral side of the forearm and filling it with a 10 mM solution of bretylium tosylate dissolved in nonconducting and nontoxic propylene glycol. In the solution, only bretylium was a conductant so that the current and duration of application proportionally mediated the amount of drug delivered. The total current density was 400 $\mu A/cm^2$ for 10 min. Further research was conducted following the same protocol and all

where successful in achieving vasoconstrictor blockade (Crandall et al., 1998; Kellogg et al., 1991a; 1991b; 1993; 1998a; Pérgola et al., 1993; 1994). Thomas et al. (1999) used a different method of iontophoresis dissolving 100mM of bretylium tosylate in doubly distilled water (18.3 MΩ·cm) and using alternating current over a 3 cm^2 area of skin over 40 min. As with previous methods, they added a control site where iontophoresis of doubly distilled water was performed to confirm intact vasodilator and vasoconstritor tone. In 2001, Mack et al. modified the original technique by replacing the Plexiglas chamber by a 3.1 cm^2 treatment pad soaked in 1.5 ml bretylium solution (100mM). The iontophoresis procedure consisted of 20 min at a current density of 160 $\mu A/cm^2$ followed by 20 min at 80 $\mu A/cm^2$. Similar to previous protocols, blockade of vasoconstriction was deemed successful after 60-90 min of rest followed by a cold stress test of 3 min.

Research has demonstrated the validity and effectiveness of this technique with the presence of initial vasoconstriction blockade by bretylium tosylate. Measures relative to baseline values show a fall at treated sites by an average of -0.74 ± 2.71 in cutaneous vascular conductance and by $34.4 \pm 4.77\%$ at control (untreated) sites (Kellogg et al., 1989; 1991a; 1991b; 1993; Pérgola et al., 1993). Further research using percentage changes relative to maximal CVC (CVC_{max}) have reported drops in order of $7.5 \pm 3.7\%$ at control sites along with insignificant statistical changes at iontophoresis sites (Crandall et al., 1998; Kellogg et al., 1998a; Mack et al., 2001; Pérgola et al., 1994).

CHAPTER III

ARTICLE I

Mechanisms Of Control Of Skin Blood Flow During Passive Heating Post-exercise

by

Glen P. Kenny[1], Julien Périard[1], Frank Reardon[1] and Nicole Drost[2]

[1]Faculty of Health Sciences, School of Human Kinetics, Ottawa, Canada

[2]Faculty of Medicine, University of Ottawa, Ottawa, Canada

ABSTRACT

Dynamic exercise induces a residual post-exercise increase in the core temperature threshold for cutaneous vasodilation (Th_{VD}). Skin blood flow measurements at a site at which adrenergic function was blocked via iontophoresis of bretylium (treated) and at an unblocked site (untreated) where performed to identify whether this shift is accomplished through the vasoconstrictor system or by the cutaneous active vasodilator system. Forearm skin blood flow was assessed by laser-Doppler flowmetry. Whole-body skin temperature (T_{sk}) was controlled by a liquid conditionned suit (LCS), and esophageal temperature (T_{es}) was monitored as an index of core temperature. Subjects either remained seated upright 15 min (no-exercise) or exercised 15 min at 75% VO_2max. Subsequently they recovered seated for 15 min afterwhich iontophoresis of bretylium was performed. Approximately 2-h after completion of the treatment, effectiveness of the blockade was assessed with a 3 min period of whole body cooling by perfusing the LCS with 2°C water. Water temperature was then raised to return T_{sk} to a normothermic level (34°C). Following the cold stress, heat stress was initiated by increasing T_{sk} with the LCS (~45 min). The core temperature at which cutaneous vasodilation began was recorded for both sites. The post-exercise Th_{VD} was similar for the untreated (36.89 ± 0.04°C) and treated (36.85 ± 0.04°C) sites respectively. The Th_{VD} in the no-exercise trials also indicate a similar response at the untreated (36.79 ± 0.05°C) and treated (36.76 ± 0.05°C) sites respectively. The similarity in response at the untreated and treated sites indicates the importance of the active vasodilator system during heat stress. However, our results indicate that the residual effect of exercise on the warm thermal response of skin blood flow is no longer manifested some 3 hours post-exercise.

Keywords: active vasoconstriction, active vasodilation, bretylium, cutaneous vascular conductance, exercise, iontophoresis, laser-Doppler flowmetry, thermoregulation

INTRODUCTION

Our recent studies indicate that exercise induces a residual effect on thermal control by increasing (~0.3-0.4°C) the post-exercise esophageal temperature onset threshold for cutaneous vasodilation (Th_{VD}) (1,2). Although the mechanism(s) for thermoregulatory control of skin blood flow prior to and during exercise have been described, post-exercise regulation remains unclear. It is well documented that the active vasodilator control of cutaneous circulation is a major mechanism for increasing skin blood flow during heat stress (3,4). Activation of the active vasodilator system is responsible for 80-95% of the elevation in skin blood flow accompanying heat stress (4).

While the active cutaneous vasodilator system is known to function as an efferent limb of thermoregulatory reflexes, recent studies clearly identify its participation in non-thermoregulatory reflexes, such as blood pressure regulation (5,6,7). These studies showed that the cutaneous vasodilator system is subject to baroreflex modulation (5,6,7). Dynamic exercise is known to cause post-exercise hypotension (8). Although the exact mechanism(s) responsible for post-exercise hypotension remain undetermined, it has been shown that acute reductions in central venous pressure delay or decrease the rise in skin blood flow during heat stress (7,9). Thus it is possible that the post-exercise increase in Th_{VD} (1,2) is related to the fact that the control of skin blood flow following exercise is subject to significant modifications by non-thermoregulatory baroreceptor reflex. In recent studies, we have shown that the non-thermal baroreceptor response to post-exercise venous blood pooling significantly influences cutaneous vasomotor control during exercise recovery (2,10). Specifically, the modification of post-exercise venous pooling, either by head down tilt (2) or by lower body positive pressure (10) results in a lowering of the resting post-exercise elevation in Th_{VD}. This baroreceptor response on

cutaneous vascular tone would be manifested in either an activation of sympathetic adrenergic vasoconstrictor activity or a withdrawal of active vasodilator activity. The following study was conducted to evaluate the mechanism of skin blood flow control during the post-exercise period. Skin blood flow monitoring with laser-Doppler flowmetry was combined with the local iontophoresis of bretylium to study the roles of the vasoconstrictor and vasodilator systems postexercise.

METHODOLOGY

With approval from the Faculty of Health Sciences Human Ethics Committee, 7 healthy subjects (2 females) participated in the study. All participants were physically active and had a mean aerobic capacity of 48.9 ± 1.57 and a percent body fat of 12.5 ± 0.73%. Subjects (mean ± SE) were 23 ± 1 years of age, 171.5 ± 1.17 cm tall, and weighed 67.8 ± 1.69 kg. The female subjects were eumenorrheic with regular, approximately 28-d long menstrual cycles. To control for hormonal effects the female subject was studied within 9-d after start of menstruation (follicular phase).

Esophageal temperature (T_{es}) was measured using a thermocouple temperature probe inserted through a nostril, into the esophagus to the level of the heart. Whole-body mean skin temperature (T_{sk}) and heat flux were measured using waterproofed temperature and heat flow sensor with integral linear thermocouple placed at 12 surface sites. The area-weighted mean was calculated by assigning the following regional percentages: head 6%, chest 9.5%, upper back 9.5%, upper arm 9%, forearm 6%, abdomen 9.5%, lower back 9.5%, anterior thigh 10%, posterior thigh 10%, anterior calf 9.5%, posterior calf 9.5%, and finger 2%.

Skin blood flow (SkBF) was measured from the left mid-anterior forearm at 2 sites separated by a distance of approximately 10 cm by laser-Doppler flowmetry (Perimed, PeriFlux System 5000). Mean arterial pressure (MAP) was continuously recorded from the electrical integration of the pulsatile blood pressure signal obtained from the middle digit (Ohmeda, Finapres 2300). Mean arterial pressure was computed from the blood pressure measurements as the diastolic pressure plus one-third of the pulse pressure. Cutaneous vascular conductance (CVC) was calculated as LDF value/MAP (volts/mmHg). Heart rate (HR) was measured, beat-by-beat, using a Polar coded transmitter and recorded continuously with a Polar Advantage interface (Polar Electro, Finland).

In all experimental trials, iontophoresis was accomplished using a Perilont Micropharmacology System PF480-1 (Perimed AB, Stockholm, Sweden). Perilont has disposable drug delivery electrode (PF 481-1) in which the drug, 10mM solution of bretylium tosylate dissolved in 100% propylene glycol, is absorbed. This design is unique and differs from the present technique of iontophoresis which utilizes a reusable chamber filled with the drug in solution. The disposable delivery electrode is embedded in a plastic chamber and fixed to the laser Doppler probe head. The probe head is then fixed to the measuring site on the ventral surface of the forearm, devoid of any superficial veins, using double-sided tape. The iontophoresis protocol consisted of 20 min at a current density of 0.4 mA followed by 10 min at a current density of 0.3 mA. Effective α-adrenergic blockade was tested 120 min after iontophoresis by cooling the entire skin surface (except feet, hands, and the local skin site on the forearm) and recording the skin blood flow and arterial blood pressure.

Subjects performed one incremental maximal VO_2 test on a cycle ergometer on the first day. These data were used to select the workload for the submaximal experimental exercise trial. Each subject was then required to perform a total of 2 experimental trials that were carried out in a random order. Upon arrival at the laboratory, subjects clothed in shorts and running shoes, were instrumented appropriately. Subjects were seated in a temperature controlled chamber at an ambient temperature of 26°C for a minimum of 10 min baseline resting. Subjects then either: 1) remained seated resting for 30 minutes (Control) or, 2) exercised on a treadmill for 15 min at 75% VO_2max (Exercise) followed by 15 min of seated rest. They were then outfitted with a liquid conditionned suit that covered the entire body except the face, fingers and feet. A spandex pant, cotton sweatshirt and cotton head cover was worn over the liquid conditionned suit. Next, iontoporesis of the selected area of skin on the ventral forearm was begun. Laser-Doppler flowmetry probes were placed on both the bretylium treated and an untreated forearm sites.

Subject remained upright seated for 2-h after the completion of iontophoresis. During this period the antiadrenergic effects of the bretylium developed. In order to verify that the α-adrenergic blockade was successful mean skin temperature was first held at 34°C with the aid of the liquid perfused garment perfused with 34°C water. The water perfusing the garment was rapidly changed to 2°C, and skin cooling continued for 3 min. Changes in CVC at each skin site were calculated by dividing the laser-Doppler flux reading by arterial blood pressure measured non-invasively. Ambient temperature was then increased to 29°C. In addition, mean skin temperature was increased at a constant rate of ~5.0°C·hr^{-1} as the temperature of the water perfusing the suit was progressively

increased until cutaneous vasodilation occurred. Following the heat stress, subjects were returned to normothermia. After skin blood flow values and esophageal temperature had returned to control levels, a second cold stress test was repeated to verify persistent α-adrenergic blockade.

To compare thresholds between conditions in which both esophageal and mean skin temperatures were changing, the following equation was used to correct the T_{es} [T_{es}(calculated)] for a designated skin temperature [T_{sk}(designated)]: T_{es}(calculated) = T_{es} + [β/(1-β)][T_{sk} -T_{sk}(designated)] (11). β= fractional contribution of the skin to the vasodilation (β=0.2) (12). The threshold esophageal temperature for cutaneous vasodilation was defined as the esophageal temperature at which there was an increase in CVC. characterized by rapid increases in CVC over three consecutive measurements. A two-way ANOVA was used to the compare the esophageal temperature threshold for cutaneous vasodilation. Data are presented as means ± SE.

RESULTS

The presence of initial vasoconstrictor blockade by bretylium inotophoresis was demonstrated by cold stress application at the start and end of the study. Untreated sites showed falls in CVC of 38.5 ± 2.0% and 39.7 ± 2.14% for the Control and Exercise trials respectively ($P < 0.0001$) while CVC at the bretylium-treated site did not change significantly (4.3 ± 1.74% and 9.7 ± 1.74% for Control and Exercise respectively). These responses, between untreated and treated sites, were significantly different from each other ($P<0.001$).

All sites showed significant vasodilation during heat stress regardless of the treatment. The esophageal temperature required to elicit cutaneous vasodilation was similar for both the treated (36.85°C) and untreated (36.88°C) sites for the Exercise condition (Table 1). Similarly no differences were measured for the Control trial for the treated (36.76°C) and untreated (36.79°C) sites respectively. There were no inter-condition differences.

Verification of α-adrenergic blockage was performed at the end of warming. Following the heat stress, subjects were returned to normothermia. After skin blood flow and core temperature had returned to baseline values, a cold stress was repeated. At the untreated site CVC fell by 46.2 ± 1.43% and 47.5 ± 1.16% for the Control and Exercise trials respectively. CVC remained unchanged at the bretylium-treated site for both the Control and Exercise trials (0.9 ± 0.97% and 2.3 ± 1.36%). The responses at the untreated and treated sites differed significantly.

DISCUSSION

Our important observation from this study was the similarity between the post-exercise Th_{VD} for the treated and untreated forearm sites. As previously indicated, we have demonstrated that exercise induces a residual post-exercise increase in Th_{VD} (1,2). However, the mechanism of control for this post-exercise shift in Th_{VD} remained unclear.

The existence of dual efferent neural control of skin blood flow allows at least cutaneous vascular tone would be manifest in either an activation of sympathetic adrenergic vasoconstrictor nerves or in a withdrawal of active vasodilator activity or a combination of both. Our demonstration of a similar Th_{VD} at the untreated and bretylium

treated forearm sites would suggest that the primary mechanism of control for the increase in the threshold for cutaneous vasodilation would be due to an attenuation of active vasodilatory response. However, as our results demonstrate, unlike our previous findings we did not demonstrate an increase in the post-exercise Th_{VD}. Although there was a slight increase in the post-exercise Th_{VD} of 0.1°C when compared to the no-exercise (Control) trial at the untreated sites, the threshold values were not significantly different. Our previous studies have demonstrated an increase of Th_{VD} by as much as 0.3-0.4°C (1,2). It is noteworthy that in these studies, the significant increase in Th_{VD} was measured as long as ~1.5-2.0-h post-exercise. However, due to technical limitations associated with the iontophoresis procedure, onset of cutaneous vasodilation was measured ~2.5-3.0-h post-exercise. These findings do provide valuable insight with respect to the residual effect of exercise on the warm thermal response of cutaneous vasodilation. It is evident from our findings that the post-exercise upward shift in Th_{VD} is no longer manifested some 3 hours post-exercise. Our observation of similar Th_{VD} at all sites confirms the important role that active vasodilator control of cutaneous circulation plays in increasing skin blood flow during heat stress, however, further studies are required to evaluate the mechanism of skin blood flow control during the post-exercise elevation of Th_{VD}.

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TALBE LEGEND

Table 1. Mean esophageal temperature threshold values for cutaneous vasodilation. T_{sk} (calculated) was set as the average T_{sk} at rest for all conditions (35.5°C).

Table 1.

	CONTROL			EXERCISE		
	T_{sk} (°C)	T_{es} (°C)	$T_{es(calculated)}$ (°C)	T_{sk} (°C)	T_{es} (°C)	$T_{es(calculated)}$ (°C)
Untreated	35.71 ± 0.09	36.74 ± 0.04	36.79 ± 0.05	35.52 ± 0.08	36.88 ± 0.03	36.89 ± 0.04
Treated	35.44 ± 0.10	36.78 ± 0.04	36.76 ± 0.05	35.42 ± 0.06	36.87 ± 0.03	36.85 ± 0.04

Esophageal temperature (T_{es}); Mean skin temperature (T_{sk}).

CHAPTER IV

ARTICLE II

Mechanism Of Control Of Skin Blood Flow Post-Exercise

by

Julien D. Périard (B.Sc., B.Ed),

Frank Reardon (Ph.D.) and Glen Kenny (Ph.D.)

University of Ottawa, Faculty of Health Sciences,
School of Human Kinetics, Human Performance and
Environmental Medicine Research Laboratory,
Ottawa, Ontario, Canada, K1N 6N5

ABSTRACT

Exercise induces a residual post-exercise increase in the core temperature threshold at which cutaneous vasodilation begins. To find whether this shift is accomplished through the vasoconstrictor system or by the cutaneous active vasodilator system, increases in skin blood flow (laser-Doppler flowmetry) at skin sites with and without α-adrenergic vasoconstrictor activity (vasodilator only) and in arterial blood pressure (non-invasive) were measured and used to calculate cutaneous vascular conductance (CVC). A single forearm site was iontophoretically treated with bretylium tosylate. The effectiveness of the bretylium treatment was assessed with a 3 min period of whole body cooling accomplished by perfusing a liquid conditioned suit with 2°C water. Esophageal temperature was monitored as an index of core temperature. Subjects either remained upright seated (no-exercise) or performed 15 min treadmill running at 70% VO_2max (exercise) followed by 20 min seated recovery. Subsequently the skin was heated (~5.0°C.hr^{-1}) and local skin temperature was maintained at 34°C until cutaneous vasodilation occurred. The core temperature at which cutaneous vasodilation began was recorded for both sites. The post-exercise core temperature threshold for cutaneous vasodilation was similar for the untreated and bretylium-treated sites which were 37.20 ±0.06°C and 37.19±0.05°C, respectively. These values were significantly elevated above no-exercise for both the untreated (36.79±0.05°C) and bretylium-treated (36.80±0.06°C) sites respectively. The similarity in response at the untreated and bretylium-treated sites indicates that the post-exercise attenuation of skin blood flow is not an α_1-adrenergically mediated constrictor response but rather, may be related to an alteration in active vasodilation.

Keywords: active vasoconstriction, active vasodilation, bretylium, cutaneous vascular conductance, exercise, iontophoresis, laser-Doppler flowmetry, thermoregulation

INTRODUCTION

The control of skin blood flow (SkBF) in the face of thermal stress is influenced by the integrated signal from both cutaneous thermoreceptors and baroreceptors (9). The autonomic effector response by the temperature regulatory center to the thermal input has a significant impact on the cardiovascular system. Initially, thermoregulatory reflexes determine the magnitude of increase in SkBF required to meet the heat dissipating demands of the thermal stress. This reflexive increase in SkBF leads to blood pooling in the cutaneous circulation and a subsequent reduction in central blood volume, thus activating cardiovascular reflexes (baroreflexes) (9). Upright dynamic exercise provides not only an endogenous thermal challenge, but also a post-exercise orthostatic challenge. This effect has been previously noted by a post-exercise hypotensive period (1,16,17,27). In these conditions where thermal and orthostatic stress are high, baroreflexes are unloaded which act to re-establish central blood volume and arterial blood pressure.

Recent studies have demonstrated that exercise induces a residual effect on post-exercise heat loss responses by increasing the post-exercise resting threshold for cutaneous vasodilation (Th_{VD}) and sweating (15). Although the mechanism(s) for thermoregulatory control of SkBF prior to and during exercise have been described, post-exercise regulation remains unclear. It is known however that the cutaneous vasodilator system is subject to baroreflex modulation (2,7,9,10,33). Cutaneous vascular tone is a determinant of blood flow and blood pressure regulation during both exercise and upright posture (28). Dynamic exercise is known to cause post-exercise hypotension (1,16,17,27). Although the exacting mechanism(s) responsible for the post-exercise hypotension remain undetermined, it has been shown that acute reductions in central venous pressure delay or decrease the rise in cutaneous blood flow during heat stress (18,23). Thus a

reasonable postulate for the post-exercise increase in the threshold for cutaneous vasodilation (15) is that the control of SkBF following exercise is subject to significant modifications by non-thermoregulatory baroreceptor reflexes.

In recent studies, it has been shown that the non-thermal baroreceptor response to post-exercise venous blood pooling significantly influences cutaneous vasomotor control during exercise recovery (6,14). Specifically, the modification of post-exercise venous pooling, either by head down tilt or by lower body positive pressure results in a lowering of the resting post-exercise elevation in Th_{VD}. This baroreceptor response on cutaneous vascular tone would be manifested in either an activation of sympathetic α-adrenergic vasoconstrictor nerves or in a withdrawal of active vasodilator activity.

Kellogg et al. (11) employed a combination of laser-Doppler flowmetry with the local iontophoresis of the antiadrenergic agent bretylium tosylate to separate vasoconstrictor and vasodilator control of the cutaneous vasculature. With the use of this technique, baroreceptor unloading was found to cause a cutaneous vasoconstriction by enhancing vasoconstrictor activity in normothermia but by reducing active vasodilatory tone in hyperthermia. The following study will employ the aforementioned technique to study the mechanism of cutaneous vascular control during the post-exercise period which is known to cause a post-exercise hypotension (i.e., baroreceptor unloading) and result in a sustained elevation of core temperature (i.e., hyperthermia).

METHODOLOGY

Subjects

Upon approval from the Faculty of Health Sciences Human Ethics Committee, 9 healthy subjects (1 female) participated in the study after providing written, informed

consent. All participants were physically active and had no history of cardiovascular or respiratory disease. Subjects (mean ± SE) were 22 ± 1 years of age, 172.11 ± 2.74 cm tall, weighed 67.72 ± 2.32 kg, had a mean aerobic capacity of 62.36 ± 2.01 ($ml \cdot kg^{-1} min^{-1}$) and a body fat of 11.06 ± 1.57 %. The female subject was eumenorrheic with regular, approximately 28-d long menstrual cycles. To control for hormonal effects the female subject was studied within 9-d after start of menstruation (follicular phase).

Instrumentation

Esophageal temperature (T_{es}) was measured using a thermocouple temperature probe inserted through a nostril, into the esophagus to the level of the heart. Skin temperature was monitored at 12 sites by Type T thermocouples integrated into heat-flow sensors (Concept Engineering, Old Saybrook, CT). The area-weighed mean skin temperature (T_{sk}) and mean heat loss (H_{sk}) were calculated by assigning the following regional percentages: head 6%, chest 9.5%, upper back 9.5%, upper arm 9%, forearm 6%, abdomen 9.5%, lower back 9.5%, anterior thigh 10%, posterior thigh 10%, anterior calf 9.5%, posterior calf 9.5%, and finger 2% (5).

Skin blood flow was measured from the left mid-anterior forearm at 2 sites separated by a distance of approximately 10 cm by laser-Doppler flowmetry (LDF) (PeriFlux System 5000, Perimed AB, Stockholm, Sweden). The laser-Doppler probes (PR 401Angled Probe, Perimed AB) were placed within a thermostatic probe holder (PF 4005-2, PeriTemp Tissue Heater). Local skin temperature was then controlled using a temperature control unit (PF5020, Perimed AB). Local skin temperature was controlled at 34°C during the experimental trial to ensure that SkBF changes were due to reflex rather then local mechanisms (30). Mean arterial pressure (MAP) was continuously

recorded from the electrical integration of the pulsatile blood pressure signal obtained from the middle digit (Ohmeda, Finapres 2300). Mean arterial pressure was computed from the blood pressure measurements as the diastolic pressure plus one-third of the pulse pressure. Cutaneous vascular conductance (CVC) was calculated as LDF value/MAP (volts/mmHg). Heart rate (HR) was measured using a Polar heart rate monitor (Vantage NV).

Iontophoresis was accomplished using a Perilont Micropharmacology System PF480-1 (Perimed AB, Stockholm, Sweden). Perilont has disposable drug delivery electrodes (PF 481-1) in which the drug, a 10mM solution of bretylium tosylate dissolved in 100% propylene glycol, is absorbed. This design is unique and differs from the present technique of iontophoresis which utilizes a reusable chamber filled with the drug in solution. The disposable delivery electrode is embedded in a plastic chamber and fixed to the laser-Doppler probe head. The probe head is then fixed to the measuring site on the ventral surface of the forearm, devoid of any superficial veins, using double-sided tape. The iontophoresis protocol consisted of 10 min at a current density of 400 $\mu A/cm^2$ (12).

Temperatures were collected and digitized (Hewlett Packard data acquisition module, model 3497A) at 5-s intervals, simultaneously displayed and recorded in spreadsheet format on a hard disk (Hewlett Packard, model PC-312, 9000).

Experimental protocol

The experimental trials were conducted in the morning at the same time of day for each subject and spaced a minimum 72-h apart. Subjects arrived following a 24-h period without heavy or prolonged physical activity, the last 12-h of which included abstinence from stimulants and alcohol, 8-h of sleep and a minimum of 0.25 l of water ingestion during each waking hour. On each study day care was taken to avoid major thermal

stimuli or substantial increase of metabolic rate between awakening and the start of the experiment.

Subjects performed one incremental maximal VO_2 test on a treadmill on the first day. These data were used to select the workload for the sub-maximal experimental exercise trials. Each subject was then required to perform a total of 2 experimental trials that were carried out in random order. On their arrival in the laboratory subjects clothed in shorts and athletic shoes were fitted with the appropriate instruments and donned a liquid conditioned suit (Three Piece Delta Temax, Pembroke, ON, Canada) covering the torso, arms and head. The ventral surface of the forearm was then prepared for the iontophoresis procedure. The laser-Doppler flow probes were taped to cleaned skin, in an area that superficially, did not appear to be highly vascular and where consistent readings were noted (19). Following the completion of the iontophoresis, subjects remained seated upright for 1-h during which time the antiadrenergic effects of the bretylium developed.

A schematic representation of the experimental timeline is presented in figure 1. Each of the two experimental trials began with a 15 min rest period with subjects seated in a temperature controlled chamber (24°C) during which baseline measurements were taken (baseline resting). During this time a 34°C water perfusion was started through the liquid conditioned suit by using a temperature-controlled circulation bath (Endocal, Neslab; and model 200-00, Micropump, WA). The temperate water perfusion was performed to control and stabilize skin and core temperature. In order to verify the α–adrenergic blockade was successful, the water perfusing the garment was rapidly changed to 2°C, and skin cooling continued for 3 minutes. Changes in CVC at each skin site were then calculated and used to verify the effectiveness of α-adrenergic blockade (20,26) prior

to the continuation of the experimental trial. Following the cooling phase, the liquid conditioned suit was removed. The subject then either exercised (exercise) or remained resting (no-exercise) in an environmental chamber at 24°C (treatment phase). For the exercise treatment the subjects performed 15 min of treadmill running at 70% of their predetermined VO_2max. For the no-exercise treatment the subjects were instructed to remain resting in a seated upright position for 15 min. Immediately following these respective treatments, subjects either remained upright seated (no-exercise) or were placed similarly seated (exercise) for 20 min (post-exercise recovery phase). Subjects were donned with the liquid conditioned suit after which mean skin temperature was increased at a rate of 4.0 ± 0.6°C·hr^{-1} as the water circulating through the suit was increased to 48°C. Whole-body warming was continued until cutaneous vasodilation was noted (warming phase). At the end of each experiment, local skin temperature at the untreated and bretylium-treated skin sites was raised to 43°C. After ~30 min of local heating, peak CVC was determined (20). Local warming was immediately followed by a second 3 min cold stress to verify the persistence of the α-adrenergic blockade.

Analysis of results

Data are presented as means ± SE. The untreated and bretylium-treated sites are reported as percentage of peak calculated from the highest 1 min average recorded during local warming. For analysis, data were normalized using the following formula: 100 x (CVC/CVC_{max}). This normalization allows the comparison of the magnitude of the changes in SkBF between different skin sites (26). Changes in CVC to cold stress were analysed by paired *t*-test comparing the levels of CVC during the last minute of cold stress with the last 5 min of the normothermic baseline. During whole-body warming, the threshold esophageal

temperature for cutaneous vasodilation was defined as the esophageal temperature at which there was an increase in CVC characterized by a sustained rise over three consecutive measurements (20). Thermal sensitivity was defined by the slope of the linear portion of the CVC-esophageal temperature relationship. The linear portion of the data was selected by visual inspection, and slopes were determined by least square linear regression analysis (20). A two-way ANOVA was used to compare the Th_{VD} between untreated and treated sites. In the event of statistical significance, ($p<0.05$), a Tukey's test was used to identify significant differences.

RESULTS

α-Adrenergic blockade

The presence of initial vasoconstriction blockade by bretylium iontophoresis was demonstrated by cold stress application at the start of the study. A significant reduction in CVC occured at the untreated skin site before (24.58 ± 3.23 to 11.80 ± 1.80% CVC_{max}; $p<0.05$) and after (96.53 ± 2.02 to 67.54 ± 1.57% CVC_{max}; $p<0.05$) the experiemntal protocol. In contrast, iontophoresis of bretylium abolished the vasoconstrictor effect of cold stress by blocking cold-induced reductions in CVC at the beginning (37.38 ± 5.20 to 38.59 ± 5.82% CVC_{max}) and at the end (97.35 ± 0.76 to 97.32 ± 0.43% CVC_{max}) of the study demonstrating the effectiveness of sympathetic vasoconstrictor blockade.

Resting T_{es} was 36.73 ± 0.03 and 36.82 ± 0.06°C and T_{sk} was 33.68 ± 0.15 and 33.67 ± 0.14°C for the no-exercise and exercsie conditions respectively. These were not significantly different in any condition and remained stable and consistent under all conditions during the 15 min baseline resting period.

Core temperature, HR and MAP response – Treatment and Post-treatment phases

Core temperature remained stable and unchanged from baseline resting during the subsequent rapid cooling phase (i.e., 3 min whole-body cooling) and 15 min of upright seated rest for the no-exercise condition. During the exercise condition, core temperature remained stable and unchanged from baseline resting and throughout the rapid cooling phase. Core temperature increased by 0.96°C above baseline resting during the 70% exercise bout. Exercise resulted in a post-exercise elevated T_{es} of ~0.4°C within the first 5 min of recovery. The post-exercise elevation in T_{es} was maintained for the 20 min recovery period.

Following an initial rise, heart rate reached a maximal plateau during the last three minutes of exercise. The end-exercise heart rate for the 70% VO_2max exercise trial was 177.22 ± 3.63 beats/min. Exercise resulted in a significantly elevated HR as the no-exercise HR following the 15 min upright sitting rest phase was 88.56 ± 1.36 beats/min ($p<0.05$).

Post-exercise MAP was significantly lower (i.e., 7.23 ± 1.55 mmHg) than baseline resting MAP for the exercise condition ($p<0.05$). In contrast, MAP did not change from rest to the end of the experiment in the no-exercise condition.

Thermoregulatory response –warming phase

Core temperature at the end of the 20 min post-exercise resting recovery was significantly elevated above no-exercise (i.e., 36.74 ± 0.04 and 37.21 ± 0.06°C for no-exercise and exercise respectively, $p<0.05$) while no significant difference was measured in T_{sk} (i.e., 33.68 ± 0.08 and 34.18 ± 0.23°C for no-exercise and exercise conditions respectively). The rate of warming for the suit perfusate (~19°C·hr^{-1}) was similar for all

groups and mean skin temperature was increased at the same rate of 4.0 ± 0.6 °C·hr^{-1} for all subjects in all conditions. The T_{sk} equivalent at the onset of cutaneous vasodilation for the untreated and bretylium-treated sites were not significantly different. T_{sk} measured 36.00 ± 0.11 and 36.22 ± 0.13 °C at the untreated site for the no-exercise and exercise trials respectively. Comparable values were measured for the bretylium-treated site (i.e., 36.08 ± 0.08 and 36.24 ± 0.12°C for no-exercise and exercise respectively). However, T_{sk} was significantly elevated above baseline resting for all conditions.

Cutaneous vasodilation

The mean T_{es} thresholds for cutaneous vasodilation for no-exercise and exercise are presented in figure 2. Following exercise, the increase in T_{es} required to elicit forearm cutaneous vasodilation was significantly higher for both the untreated (0.39°C) and bretylium treated (0.37°C) sites in comparison to the no-exercise trial ($p<0.05$). Th_{VD} values for both the no-exercise (36.79±0.05 and 36.80±0.06) and exercise trials (37.18 ± 0.04 and 37.17 ± 0.04) were similar for the untreated and bretylium-treated respectively (Table 1).

The sensitivity of the post-exercise thermal reflex was estimated from the slope of the linear relationship between CVC and T_{es}. The rate of rise of CVC per unit T_{es} was not significantly altered with the application of bretylium (i.e., vasodilator only site) in both the no-exercise and exercise treatment conditions. Further, there were no differences in the slope of the linear relationship between CVC and T_{es} between no-exercise and exercise for both the untreated and bretylium treated sites. The vasodilator sensitivity averaged 85.90 ± 6.54%/°C and 90.85 ± 6.38%/°C for exercise for the untreated and bretylium treated sites respectively. Similarly no differences in the slopes were measured

between untreated (86.70 ± 5.74%/°C) and bretylium-treated (88.10 ± 5.26%/°C) sites for the no-exercise trial.

DISCUSSION

The following study is the first to examine the mechanism of control of post-exercise SkBF. The major finding of this study was the demonstration that exercise can have a residual influence over the cutaneous vasodilator system as evidenced by our observation that the esophageal temperature thresholds for cutaneous vasodilation were higher during exercise at both bretylium-treated and untreated sites. The thresholds for cutaneous vasodilation during no-exercise and exercise were not statistically different between untreated and bretylium-treated sites. The lack of disparity between the thresholds for vasodilation at bretylium-treated and untreated sites during the post-exercise recovery period implies little or no role for the active vasoconsctrictor system in the increase of Th_{VD} during the post-exercise resting period. Further, the post-exercise increase in the esophageal temperature threshold for cutaneous vasodilation (0.4°C), as measured at the untreated site, confirms our previous findings of a post-exercise increase in warm response thresholds (15).

The post-exercise increase in esophageal temperature thresholds measured at both the bretylium-treated and untreated sites were not caused by differences in rate of change of esophageal temperature or mean skin temperature, as warming rates were not significantly different from the no-exercise experimental trial. In addition all trials for both no-exercise and exercise were conducted at the same time of day. Therefore, the increase in the post-exercise threshold for cutaneous vasodilation is unlikely due to a circadian shift in set-point.

Studies have shown that hypohydration increases the threshold for cutaneous vasodilation (3) and that the magnitude of the response for SkBF is dependent on the level of dehydration (3). Although we did not quantify the hydration status of our subjects, it is unlikely that any significant hypohydration occurred. Montain and Coyle (22) demonstrated that 2-h of heavy dynamic exercise in a warm environment (33°C) with no water intake results in a maximum weight loss of 4.2%. Therefore, in our study the short period of exercise (only 15 min) in a cooler environment (24°C) with unrestricted pre-trial water intake, is unlikely to have caused more than a 0.5% weight loss. Under this condition, our subjects could be considered euhydrated (4).

During exercise itself, the threshold for cutaneous vasodilation has been shown to increase (10,13,29,32). The magnitude of the increase is dependent upon ambient temperature (25) and exercise intensity (29,31), with cutaneous vasodilation significantly delayed or absent at intensities beyond 80% VO_2max. Previous research has suggested that baroreceptor modulation is responsible for the measured increase in the threshold for cutaneous vasodilation observed during exercise (8, 11, 29, 31). It has been demonstrated that the cutaneous circulation is on the efferent limb of several non-thermoregulatory reflexes, including the baroreceptor reflex (2,9,10,33). Baroreceptor unloading has been shown to cause cutaneous vasoconstriction. Studies involving head-up tilt (24) and lower body negative pressure (21,33) manoeuvres that displace blood volume to legs, have proven to evoke cutaneous vasoconstrictor activity in resting humans. Kellogg et al. (11) were able to demonstrate that during whole-body heating under normal resting conditions baroreceptor unloading caused a withdrawal of active cutaneous vasodilation. A similar non-thermal baroreflex modulation of cutaneous SkBF has been demonstrated during exercise. Mack et al. (20) showed that baroreceptor unloading induced by the application

of -40 mmHg lower body negative pressure during exercise attenuated the threshold for cutaneous vasodilation which was quickly reversed when the lower body negative pressure was removed. As observed under resting conditions, baroreceptor modulation of cutaneous vasomotor response was manifested as a baroreceptor modulation of active cutaneous vasodilatory response.

Our observation of an increase in the post-exercise threshold may in fact parallel the response observed during whole-body warming at rest and exercise. It is well documented that cutaneous vascular tone is a determinant of blood flow and blood pressure regulation during both exercise and upright posture (28). Dynamic exercise is known to cause post-exercise hypotension (1,16,17). Although the exact mechanism(s) responsible for post-exercise hypotension remain undetermined, it has been shown that acute reductions in central venous pressure delay or decrease the rise in skin blood flow during heat stress (18,23). Thus a plausible explanation for the post-exercise increase in Th_{VD} may relate to the fact that the control of skin blood flow following exercise is subject to significant modifications by non-thermoregulatory baroreceptor reflex via an attenuation of the active cutaneous vasodilatory response.

It is known that the resistance vessels in exercised skeletal muscle remain dilated after a bout of dynamic exercise and the hyperemia in this region tends to persist well into recovery (27). It is likely that in response to post-exercise hypotension, baroreceptor mediated peripheral skin vasoconstriction is elicited. Previous work conducted in our laboratory has demonstrated that the non-thermal baroreceptor response to post-exercise venous blood pooling significantly influences cutaneous vasomotor control during exercise recovery (6,14). Specifically, the modification of post-exercise venous pooling, either by head down tilt or by lower body positive pressure resulted in a lowering of the

resting post-exercise elevation in Th_{VD}. Our current findings of a similarity in response at the untreated and bretylium-treated sites provide substantial support for the hypothesis that the interaction of baroreceptors on themoregulatory responses during exercise represents modulation of active cutaneous vasodilation and that the post-exercise attenuation of skin blood flow is not an α_1-adrenergically mediated constrictor response.

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TABLE LEGEND

Table 1. Mean esophageal temperature threshold values for the no-exercise and exercise condition for both the bretylium treated (vasodilator only) and untreated forearm skin sites. Mean skin temperature (T_{sk}); Eesophageal temperature (T_{es}).

FIGURE LEGEND

Fig. 1 Experimental protocol time line (minutes).

Fig. 2 Mean and individual resting esophageal temperature thresholds for cutaneous vasodilation for no-exercise and exercise, for the bretylium treated and untreated sites.

Table 1.

	No-exercise		Exercise	
	Untreated	**Bretylium-treated**	**Untreated**	**Bretylium-treated**
T_{es} (°C)	36.79 ± 0.05	36.80 ± 0.06	37.18 ± 0.04*	37.17 ± 0.04*
T_{sk} (°C)	36.08 ± 0.07	36.08 ± 0.08	36.22 ± 0.13	36.23 ± 0.12

* Significantly different from no-exercise $p < 0.05$

Figure 1.

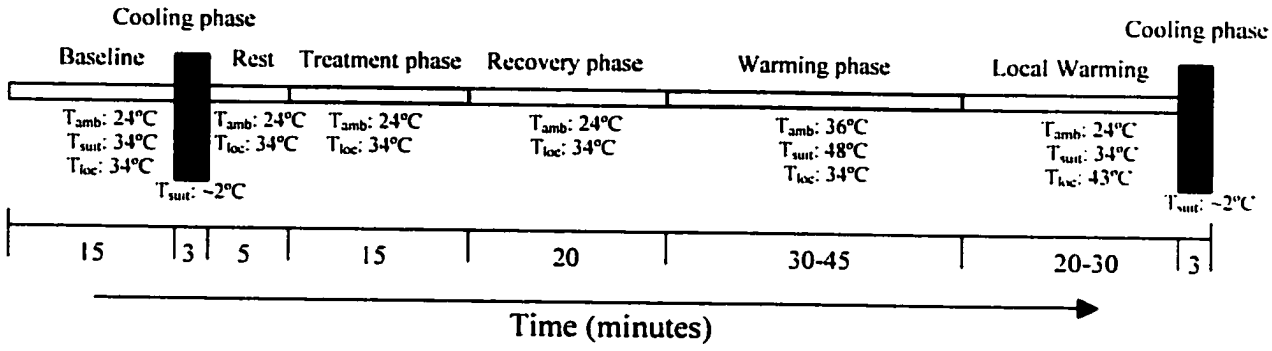
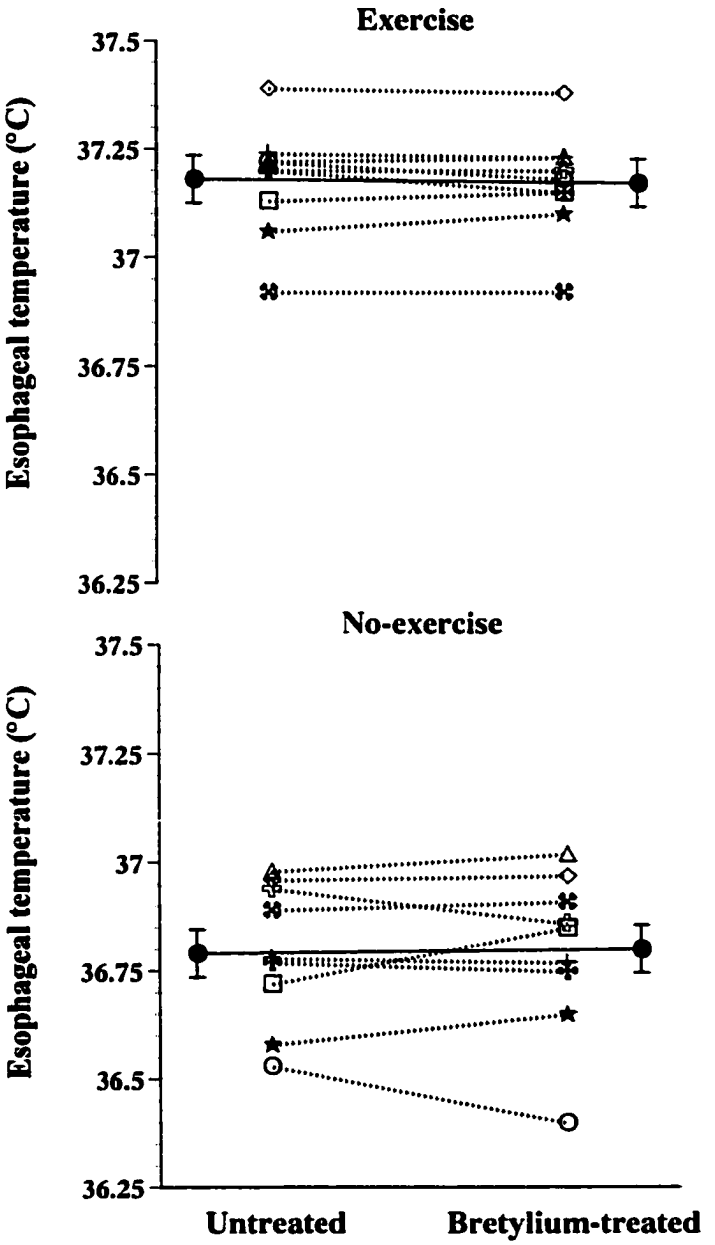

Cooling phase
Cooling phase
Baseline
Rest
Treatment phase
Recovery phase
Warming phase
Local Warming
T_{amb}: 24°C
T_{suit}: 34°C
T_{loc}: 34°C
T_{suit}: ~2°C
T_{amb}: 24°C
T_{loc}: 34°C
T_{amb}: 24°C
T_{loc}: 34°C
T_{amb}: 24°C
T_{loc}: 34°C
T_{amb}: 36°C
T_{suit}: 48°C
T_{loc}: 34°C
T_{amb}: 24°C
T_{suit}: 34°C
T_{loc}: 43°C
T_{suit}: ~2°C
15
3
5
15
20
30-45
20-30
3
Time (minutes)

Figure 2.


Exercise
Esophageal temperature (°C)
37.5
37.25
37
36.75
36.5
36.25
No-exercise
Esophageal temperature (°C)
37.5
37.25
37
36.75
36.5
36.25
Untreated
Bretylium-treated

CHAPTER V

ARTICLE III

The Effect Of Exercise Intensity On Post-Exercise Skin Blood Flow Control

by

Julien D. Périard (B.Sc., B.Ed).

Frank Reardon (Ph.D.) and Glen Kenny (Ph.D.)

University of Ottawa, Faculty of Health Sciences.
School of Human Kinetics, Human Performance and
Environmental Medicine Research Laboratory,
Ottawa, Ontario, Canada, K1N 6N5

ABSTRACT

The hypothesis that exercise intensity causes a parallel increase in the post-exercise onset threshold for cutaneous vasodilation (Th_{VD}) mediated by an attenuation of active vasodilator activity, was tested in nine subjects. Increases in forearm skin blood flow (laser-Doppler flowmetry) and mean arterial blood pressure were measured and used to calculate cutaneous vascular conductance at two superficial sites, one with intact α-adrenergic vasoconstrictor activity (untreated) and one infused with bretylium tosylate (bretylium-treated). The effectiveness of the bretylium treatment was assessed with a 3 min period of whole body cooling accomplished by perfusing a liquid conditioned suit with 2°C water. Esophageal temperature was monitored as an index of core temperature. Subjects performed 15 min treadmill running either at 55 (light), 70 (moderate) or 85% (intense) VO_2max followed by 20 min seated recovery. A liquid conditioned suit was used to increase mean skin temperature (~5.0°C/hr), while local forearm temperature was clamped at 34°C until cutaneous vasodilation occured. Exercise resulted in a significant elevation in the post-exercise Th_{VD} at both the untreated (36.98 ± 0.06, 37.18 ± 0.04 and 37.32 ± 0.05; $p<0.05$) and bretylium-treated (36.99 ± 0.07, 37.17 ± 0.04 and 37.33 ± 0.05; $p<0.05$) sites with increasing exercise intensity (light, moderate and intense respectively). Post-exercise Th_{VD} values for both the untreated and bretylium-treated sites were not significantly different. Mean arterial pressure decreased by 5.89, 7.23 and 11.02 mmHg for the light, moderate and intense exercise trials respectively ($p< 0.05$). It is concluded that the post-exercise increase in onset threshold for vasodilation is likely caused by an attenuation of active vasodilator activity modulated by baroreceptor reflexes in response to post-exercise hypotension.

Keywords: active vasodilation, bretylium, cutaneous vascular conductance, hypotension, iontophoresis, laser-Doppler flowmetry, mean arterial pressure, thermoregulation

INTRODUCTION

During exercise, reflex control of cutaneous circulation is mediated by both the noradrenergic vasoconstrictor and active vasodilator systems (6,15). When exercise is initiated, a reduction of skin blood flow in inactive regions provides additional blood flow to active skeletal muscle subsequent to metabolic demand. This reflex reduction in vascular conductance is accomplished solely through enhanced vasoconstrictor tone independent of thermal conditions (13, 27). As steady-state exercise is continued, a rise in core temperature stimulates cutaneous vasodilation increasing skin blood flow (SkBF) in response to the heat dissipating demands of the thermal stress (10, 26).

Johnson et al. (7,8) showed that exercise results in an elevation of the threshold for cutaneous vadodilation (Th_{VD}) above resting values. The magnitude of the increase is dependent upon ambient temperature (26) and exercise intensity (4,19,33,35), with cutaneous vasodilation significantly delayed or absent at intensities beyond 80% VO_2max (33). Subsequent studies have determined that the attenuation in the onset threshold for cutaneous vasodilation is the result of a delay in the activation of the vasodilator system manifested by a strong non-thermal baroreceptor mediated reflex control of cutaneous vascular response (14).

Thoden et al. (36) first proposed that the reduction in forearm skin blood flow and mean skin temperature (except over the exercised muscle), despite a sustained increase in the post-exercise esophageal temperature, was consistent with a sustained post-exercise increase in the vasodilation threshold. Recent studies have demonstrated that exercise induces a residual effect on post-exercise heat loss responses by increasing the post-exercise resting threshold for cutaneous vasodilation and sweating (18). Recent evidence

points to a baroreceptor mediated influence on post-exercise thermoregulatory response. Upright dynamic exercise provides not only an endogenous thermal challenge, but also a post-exercise orthostatic challenge. That is, the great degree of blood pooling in the previously active musculature provides a significant additional decrease in central blood volume. This effect has been previously noted by a post-exercise hypotensive period (1,20,21). It has been shown that acute reductions in central venous pressure delay or decrease the rise in SkBF during heat stress (22,25). Thus, a reasonable postulate for the post-exercise increase in Th_{VD} (16,29) is that SkBF control following exercise is subject to significant modifications by non-thermoregulatory baroreceptor reflexes. Manipulating post-exercise venous pooling by means of head down tilt and lower body positive pressure was shown to result in a decrease of the resting post-exercise elevation in Th_{VD} (5,16) similar to that observed during exercise (14). Périard et al. (29) showed that the post-exercise attenuation of skin blood flow is likely related to an alteration in active vasodilation and not an α_1-adrenergically mediated constrictor response.

Of interest, Kenny and Neidre (17) showed that an increase in the post-exercise hypotensive response, induced by exercise of increasing intensity, was paralleled by an increase in the magnitude of the post-exercise elevation in esophageal temperature (i.e., a difference of 0.41°C between conditions). Although they did not measure the post-exercise threshold for heat loss, they speculated that the increase in the post-exercise esophageal temperature response observed with increasing exercise intensity was due in part to an intensity dependent attenuation of the heat loss response. As such, the following study was conducted to evaluate the hypothesis that the post-exercise increase in esophageal temperature is paralleled by an increase in the heat loss response of cutaneous vasodilation. Furthermore, exercise of increasing intensity (i.e., 55, 70 and

85% VO_2max) was used in order to further study the effect of post-exercise blood pressure response on the post-exercise resting threshold for cutaneous vasodilation

METHODOLOGY

Subjects

Upon approval from the Faculty of Health Sciences Human Ethics Committee, 9 healthy subjects (1 female) participated in the study after providing written, informed consent. All participants were physically active and had no history of cardiovascular or respiratory disease. Subjects (mean ± SE) were 22 ± 1 years of age, 172.11 ± 2.74 cm tall, weighed 67.72 ± 2.32 kg, had a mean aerobic capacity of 62.36 ± 2.01 ($ml \cdot kg^{-1} min^{-1}$) and a body fat of 11.06 ± 1.57 %. The female subject was eumenorrheic with regular, approximately 28-d long menstrual cycles. To control for hormonal effects the female subject was studied within 9-d after start of menstruation (follicular phase).

Instrumentation

Esophageal temperature (T_{es}) was measured using a thermocouple temperature probe inserted through a nostril, into the esophagus to the level of the heart. Skin temperature was monitored at 12 sites by Type T thermocouples integrated into heat-flow sensors (Concept Engineering, Old Saybrook, CT). The area-weighed mean skin temperature (T_{sk}) and mean heat loss (H_{sk}) were calculated by assigning the following regional percentages: head 6%, chest 9.5%, upper back 9.5%, upper arm 9%, forearm 6%, abdomen 9.5%, lower back 9.5%, anterior thigh 10%, posterior thigh 10%, anterior calf 9.5%, posterior calf 9.5%, and finger 2% (3).

Skin blood flow was measured from the left mid-anterior forearm at 2 sites separated by a distance of approximately 10 cm by laser-Doppler flowmetry (LDF) (PeriFlux System 5000, Perimed AB, Stockholm, Sweden). The laser-Doppler probes (PR 401Angled Probe, Perimed AB) were placed within a thermostatic probe holder (PF 4005-2, PeriTemp Tissue Heater). Local skin temperature was then controlled using a temperature control unit (PF5020, Perimed AB). Local skin temperature was controlled at 34°C during the experimental trial to ensure that SkBF changes were due to reflex rather then local mechanisms (34). Mean arterial pressure (MAP) was continuously recorded from the electrical integration of the pulsatile blood pressure signal obtained from the middle digit (Ohmeda, Finapres 2300). Mean arterial pressure was computed from the blood pressure measurements as the diastolic pressure plus one-third of the pulse pressure. Cutaneous vascular conductance (CVC) was calculated as LDF value/MAP (volts/mmHg). Heart rate (HR) was measured using a Polar heart rate monitor (Vantage NV).

Iontophoresis was accomplished using a PeriIont Micropharmacology System PF480-1 (Perimed AB, Stockholm, Sweden). PeriIont has disposable drug delivery electrodes (PF 481-1) in which the drug, a 10mM solution of bretylium tosylate dissolved in 100% propylene glycol, is absorbed. This design is unique and differs from the present technique of iontophoresis which utilizes a reusable chamber filled with the drug in solution. The disposable delivery electrode is embedded in a plastic chamber and fixed to the laser-Doppler probe head. The probe head is then fixed to the measuring site on the ventral surface of the forearm, devoid of any superficial veins, using double-sided tape. The iontophoresis protocol consisted of 10 min at a current density of 400 $\mu A/cm^2$ (15).

Temperatures were collected and digitized (Hewlett Packard data acquisition module, model 3497A) at 5-s intervals, simultaneously displayed and recorded in spreadsheet format on a hard disk (Hewlett Packard, model PC-312, 9000).

Experimental protocol

The experimental trials were conducted in the morning at the same time of day for each subject and spaced a minimum 72-h apart. Subjects arrived following a 24-h period without heavy or prolonged physical activity, the last 12-h of which included abstinence from stimulants and alcohol, 8-h of sleep and a minimum of 0.25 l of water ingestion during each waking hour. On each study day care was taken to avoid major thermal stimuli or substantial increase of metabolic rate between awakening and the start of the experiment.

Subjects performed one incremental maximal VO_2 test on a treadmill on the first day. These data were used to select the workload for the sub-maximal experimental exercise trials. Each subject was then required to perform a total of 3 experimental trials that were carried out in random order. On their arrival in the laboratory subjects clothed in shorts and athletic shoes were fitted with the appropriate instruments and donned a liquid conditioned suit (Three Piece Delta Temax, Pembroke, ON, Canada) covering the torso, arms and head. The ventral surface of the forearm was then prepared for the iontophoresis procedure. The laser-Doppler flow probes were taped to cleaned skin, in an area that superficially, did not appear to be highly vascular and where consistent readings were noted (23). Following the completion of the iontophoresis, subjects remained seated upright for 1-h during which time the antiadrenergic effects of the bretylium developed.

A schematic representation of the experimental timeline is presented in figure 1. Each of the two experimental trials began with a 15 min rest period with subjects seated

in a temperature controlled chamber (24°C) during which baseline measurements were taken (baseline resting). During this time a 34°C water perfusion was started through the liquid conditioned suit by using a temperature-controlled circulation bath (Endocal, Neslab; and model 200-00, Micropump, WA). The water temperate perfusion was performed to control and stabilize skin and core temperature. In order to verify the α–adrenergic blockade was successful, the water perfusing the garment was rapidly changed to 2°C, and skin cooling continued for 3 min. Changes in CVC at each skin site were then calculated and used to verify the effectiveness of α-adrenergic blockade (24,28) prior to the continuation of the experimental trial. Following the cooling phase, the liquid conditioned suit was removed. The subject then exercised in an environmental chamber at 24°C (treatment phase). For the exercise treatment the subjects performed 15 min of treadmill running either at 55 (light), 70 (moderate) or 85% (intense) of their predetermined VO_2max. Immediately following the treatment, subjects were placed seated upright for 20 min (post-exercise recovery phase). Subjects donned a the liquid conditioned suit by means of which mean skin temperature was increased at a rate of 4.0 ± 0.6°C·hr^{-1} as the temperature of the water circulating through the suit was increased to 48°C. Whole-body warming was continued until cutaneous vasodilation was noted (warming phase). At the end of each experiment, local skin temperature at the untreated and bretylium-treated sites was raised to 43°C. After ~30 min of local heating, peak CVC was determined (24). Local warming was immediately followed by a second 3 min cold stress to verify the persistence of the α-adrenergic blockade.

Analysis of results

Data are presented as means ± SE. The untreated and bretylium-treated sites are reported as percentage of peak calculated from the highest 1-min average recorded during local warming. For analysis, data were normalized using the following formula: 100 x (CVC/CVC_{max}). This normalization allows the comparison of the magnitude of the changes in SkBF between different skin sites (28). Changes in CVC to cold stress were analysed by paired *t*-test comparing the levels of CVC during the last minute of cold stress with the last 5 min from the normothermic baseline period. During whole-body warming, the threshold esophageal temperature for cutaneous vasodilation was defined as the esophageal temperature at which there was an increase in CVC characterized by a sustained rise over three consecutive measurements (24). Thermal sensitivity was defined by the slope of the linear portion of the CVC-esophageal temperature curve. The linear portion of the data was selected by visual inspection, and slopes were determined by least square linear regression analysis (24). Two-way ANOVA was used to compare the Th_{VD} between untreated and bretylium-treated sites between the different exercise conditions. In the event of statistical significance, ($p<0.05$), a Tukey's test was used to identify significant differences.

RESULTS

α-Adrenergic blockade

The presence of initial vasoconstriction blockade by bretylium iontophoresis was demonstrated by cold stress application at the start of the study. A significant reduction in CVC occured at the untreated skin site before (28.12 ± 5.04 to 14.63 ± 3.08% CVC_{max}; $p<0.05$) and after (96.04 ± 1.51 to 68.12 ± 1.25% CVC_{max}; $p<0.05$) the experiemntal

protocol. In contrast, iontophoresis of bretylium abolished the vasoconstrictor effect of cold stress by blocking cold-induced reductions in CVC at the beginning (45.78 ± 5.50 to 46.50 ± 6.06% CVC_{max}) and at the end (97.27 ± 0.54 to 97.16 ± 0.34% CVC_{max}) of the study demonstrating the effectiveness of sympathetic vasoconstrictor blockade.

The resting T_{es} recorded during light, moderate and intense exercise were respectively 36.78 ± 0.07, 36.82 ± 0.06 and 36.65 ± 0.08°C. Similarly, the resting T_{sk} values were 33.67 ± 0.09, 33.67 ± 0.14 and 33.68 ± 0.07°C respectively. These temperatures were not significantly different between conditions and remained stable and consistent under all conditions during the 15 min baseline resting period.

Core temperature, HR and MAP response – Treatment and Post-treatment phases

Core temperature remained stable and unchanged from baseline resting during the subsequent rapid cooling phase, that is, after 3 min of whole-body cooling. Core temperature increased by 0.64, 0.96 and 1.61°C above baseline resting during the light, moderate and intense exercise bouts respectively ($p<0.05$). Exercise resulted in a post-exercise sustained elevation of esophageal temperature value of 0.3, 0.4 and 0.6°C above baseline resting for the light, moderate and intense exercise bouts respectively, within the first 5 min of recovery. The post-exercise elevation in esophageal temperature was maintained for the 20 min recovery period.

Following an initial rise, heart rate levels reached a maximal plateau during the last three minutes of exercise. The end-exercise heart rates were 157.22 ± 5.04, 177.22 ± 3.63, and 189.67 ± 1.68 beats/min for the light, moderate and intense exercise trials respectively ($p<0.05$).

For all exercise conditions, the recorded post-exercise mean arterial pressure was significantly lower than baseline rest. These values were 85.59 ± 0.91, 84.29 ± 1.49 and 81.43 ± 1.18 mmHg for the 55, 70 and 85% VO_2max exercise respectively. There appeared to be a relation between the average post-exercise mean arterial pressure and exercise intensity in that there was a decrease of 5.89, 7.23 and 11.02 mmHg for the light, moderate and intense exercise conditions respectively. A significant ($p<0.05$) difference in the post-exercise mean arterial pressure response was measured between light and intense exercise. Mean arterial pressure remained below baseline resting for the duration of the post-exercise recovery phase (Table 1).

Thermoregulatory response –warming phase

Prior to the start of warming, the esophageal temperatures for all exercise conditions were significantly elevated ($p<0.05$) above baseline. Respectively these were: 37.06 ± 0.07; 37.21 ± 0.06; and 37.30 ± 0.08°C for the light, moderate and intense exercise. Esophageal temperature for intense exercise was significantly greater than light exercise ($p<0.05$). Similarly mean skin temperatures were not different from baseline values and no differences were measured between conditions. These temperatures were respectively: 34.12 ± 0.19; 34.18 ± 0.23; and, 34.18 ± 0.18°C for light, moderate and intense exercise.

The warming of the suit perfusate at a rate of approximately ~19°C·hr^{-1} was similar for all groups and resulted in an increase in mean skin temperature at a rate of 4.0 ± 0.6 °C·hr^{-1} for all conditions. Mean skin temperatures at the onset of cutaneous vasodilation for the untreated and bretylium-treated sites were not significantly different between conditions. These values for light, moderate and intense exercise respectively for

the untreated site were 36.08 ± 0.11, 36.22 ± 0.13 and 36.23 ± 0.10 °C and for the bretylium-treated site were 36.11 ± 0.08, 36.24 ± 0.12 and 36.20 ± 0.12°C.

Cutaneous vasodilation

The mean thresholds for cutaneous vasodilation during exercise and post-exercise are presented in figure 2. The onset esophageal temperature threshold for forearm cutaneous vasodilation of exercise was significantly elevated with increasing exercise intensity for both the untreated and bretylium-treated sites ($p<0.05$). Threshold values for the untreated and bretylium-treated sites were similar for each of the respective exercise conditions (Table 2).

A pattern of increase in the onset threshold for cutaneous vasodilation during post-exercise warming was noted as exercise intensity increased for both the untreated and bretylium-treated sites. These threshold values were significantly ($p<0.05$) higher than light exercise both during moderate and intense exercises; thus, 0.20 and 0.34°C respectively for the untreated site and 0.18 and 0.34°C, for bretylium-treated site. A 0.14 and 0.16°C increase for untreated and bretylium-treated sites were registered between moderate and intense exercise ($p<0.05$).

The sensitivity of the post-exercise thermal reflex was estimated from the slope of the linear relationship between CVC and T_{es}. The rate of rise of CVC per unit T_{es} was not significantly altered with the application of bretylium (i.e., vasodilator only site). Further, there was no difference in the slope of this curve between untreated and bretylium-treated sites under all three exercise conditions. The vasodilator sensitivity for the light, moderate and intense treatment conditions averaged 91.09 ± 5.04, 85.90 ± 6.54 and 90.87

± 3.29 %/°C for untreated sites and 89.67 ± 4.44, 90.85 ± 6.38 and 93.50 ± 3.63%/°C at bretylium-treated sites respectively.

DISCUSSION

It is apparent from this study that there was a parallel increase in post-exercise esophageal temperature and in the onset threshold for cutaneous vasodilation with increasing exercise intensity at both untreated and bretylium-treated forearm sites. The observation of a graded increase in the post-exercise threshold for cutaneous vasodilation at the untreated and bretylium-treated sites is concommittant with the effect of workload on cutaneous vascular response to exercise (33,35) and confirms our previous observations of an increase in the post-exercise resting Th_{VD} following moderate intensity dynamic exercise (18,16,5). Further, the lack of vasoconstrictor response to cold stress both at the beginning and the end of the study indicates successful abolition of active vasoconstriction (15). Thus, the similarity in response between untreated and bretylium-treated sites during both the exercise and post-exercise conditions reinforces previous observations of baroreceptor modulation of active cutaneous vasodilation during exercise (14) and post-exercise (29).

It is known that the active cutaneous vasodilator system is directly affected by the reflex adjustments to dynamic exercise, as it is by the baroreceptor reflex (12,14). Of particular interest in this study was the magnitude of the post-exercise increase in Th_{VD} measured as a function of exercise intensity. Johnson and Park (8) showed that upright exercise contributed to the elevation of the threshold for vasodilation. Specifically, the net effect of exercise on the control of SkBF was to elevate the threshold for vasodilaton relative to rest. Taylor et al. (35) further demonstrated that above a critical workload of

125W, exercise governed control of peripheral vasodilation stimulates a reaction that opposes that initiated during thermoregulation by elevating the Th_{VD} in graded fashion. Thus, at high relative exercise intensities the SkBF response to dynamic exercise seems to be significantly attenuated, resulting in a reduced heat transfer and therefore a tendency to increase core temperature. The attenuation in SkBF and subsequent reduction in thermoregulatory vasodilation is caused by increasing vasoconstrictor tone as a non-thermal factor in response to increasing workload (4,35).

Earlier studies do not confirm this critical workload or graded effect of exercise intensity on the SkBF to core temperature (i.e., T_{es}) relationship (9,37). In these studies, the range of workload varied from 50 to 150W and 30 to 70% VO_2max respectively. Thus, it is possible that the exercise intensity effect could have been non-existent or of a magnitude too low to be observed in the plethysmographic data measured during these investigations.

Two latter studies did however reveal the same influence of workload on exercise. Smolander et al. (32) examined the effect of incremental exercise in normothermic and hyperthermic environments on forearm SkBF. Exercise at the heaviest workloads of 150W significantly attenuated the forearm SkBF to core temperature response indicating that exercise above a critical intensity does markedly reduce SkBF. A subsequent study using five different exercise intensities (50, 60, 70, 80 and 90% VO_2max) indicated that the lower workloads (50 to 70 %) had no significant effect on Th_{VD} or thermal sensitivity slopes for SkBF (33). However, at 80% of maximal aerobic capacity, esophageal temperature was relatively much higher than at steady state. At 90% VO_2 max there was a marked reduction in the SkBF to core temperature relationship. These non-thermal, exercise related changes suggest an attenuation of forearm SkBF response at high

exercise intensities subsequent to normal thermal reflex activity. An explanation of this attenuated rate of rise of SkBF could be related to a limitation of active vasodilator activity during the latter phase of upright exercise when core temperature approaches 38°C (11). As with earlier studies, the effect of this attenuation in SkBF on the onset threshold for vasodilation during exercise may be related to the non-thermal influence of baroreflex modulation on cutaneous vascular conductance (14,22,24).

Our observations of a graded exercise intensity effect on the control of skin blood flow during exercise are consistent with those of Smolander et al. (33) and Taylor et al. (35). In the present study, we found that the threshold for vasodilation increased in parallel with exercise intensities of 55, 70 and 85% VO_2max.

We previously demonstrated that the post-exercise increase in the esophageal temperature threshold for cutaneous vasodilation is caused by an attenuation of skin blood flow through a delay in the activation of active vasodilatory response (29). Our observation of a similar Th_{VD} at the untreated and bretylium-treated sites in the present study support the premise that the primary effect of the mechanism of control for the increase in the post-exercise Th_{VD} is an attenuation of active vasodilation. Interestingly, the pattern of elevation of the post-exercise Th_{VD} parallels the same response observed during exercise (14). These results are consistent with exercise observations that support baroreceptor modulation of cutaneous circulation (2,12,13,24). Moreover, the similarity of response between post-exercise treated and untreated thermal sensitivity slopes reinforces the theory of a central, baroreceptor modulated response as observed at rest (2) and during exercise (24). Thus, the post-exercise increase in Th_{VD} with increasing exercise intensity could be caused by a delay in the activation of the active vasodilator

system. This in turn would elevate the internal temperature threshold at which active cutaneous vasodilation begins (13).

As previously indicated, we have shown that the non-thermal baroreceptor response to post-exercise venous blood pooling significantly influences cutaneous vasomotor control during exercise recovery (16,5). Specifically, the modification of post-exercise venous pooling, either by head down tilt (16) or by lower body positive pressure (5) results in a lowering of the resting post-exercise elevation in Th_{VD}. Recently, we demonstrated that the magnitude of the post-exercise T_{es} elevation was increased by 0.41°C with increasing exercise intensity (70 and 93%VO_2max) (17). Consistent with the post-exercise increase in T_{es} response was the greater hypotension observed following higher intensity exercise, which in turn elicited significant differences in blood pressure response (30). The post-exercise hypotension was likely caused by pooling of warmed blood in the muscle (31) resulting in decreased total peripheral resistance.

Several investigations studying exercise have confirmed that cutaneous vascular response is primarily due to baroreceptor modulated withdrawal of active cutaneous vasodilation (12,13,22,24). Post-exercise warm thermal responses are also known to be under baroreceptor modulation (16,5). In the present study there appeared to be a strong baroreceptor drive, increasing with exercise intensity. Thus it is thought that the increase in Th_{VD} with higher workloads is the result of baroreceptor modulation of cutaneous vasomotor response. This occurs through withdrawal of active vasodilator activity despite acute reductions in post-exercise central venous pressure and cardiac filling. The increased exercise intensity results in a greater post-exercise hypotension and baroreceptor unloading, thus increasing the onset threshold for vasodilation.

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TABLE LEGEND

Table 1. Influence of light, moderate and intense exercise intensity on mean arterial pressure in the post-exercise recovery period (10 - 20 minutes).

Table 2. Mean esophageal temperature threshold values for the light, moderate and intense exercise conditions for both the bretylium-treated (vasodilator only) and untreated forearm skin sites. Mean skin temperature (T_{sk}); Esophageal temperature (T_{es}).

FIGURE LEGEND

Fig. 1 Experimental protocol timeline (minutes).

Fig. 2 Mean and individual resting esophageal temperature thresholds for cutaneous vasodilation for the light, moderate and intense exercise conditions, for the bretylium-treated and untreated sites.

Table 1.

	Mean arterial pressure			
	Baseline (mmHg)	**10 min Post-Ex (mmHg)**	**15 min Post-Ex (mmHg)**	**20 min Post-Ex (mmHg)**
Light	91.47 ± 1.91	84.51 ± 0.81*	85.94 ± 1.27*	85.86 ± 0.98*
Moderate	92.52 ± 1.88	83.89 ± 1.42*	83.82 ± 1.44*	84.57 ± 0.91*
Intense	92.46 ± 0.78	80.73 ± 1.03*†	81.57 ± 1.22*†	81.20 ± 1.35*†

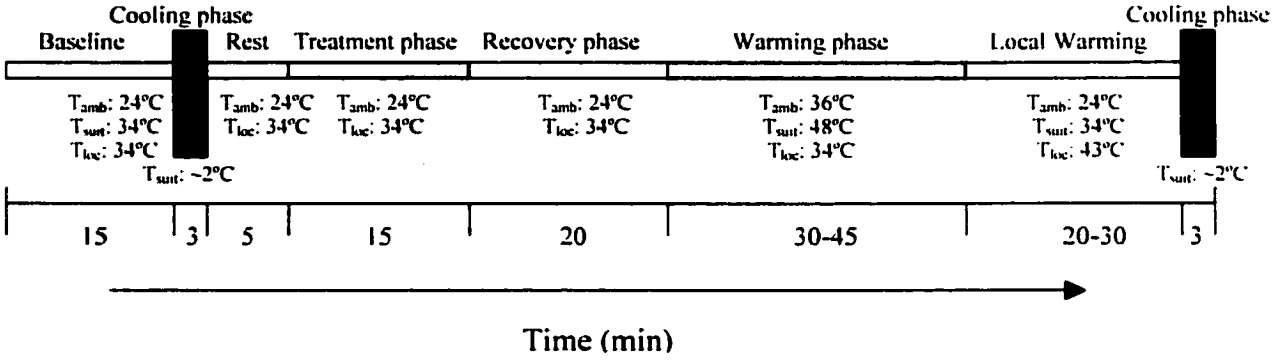
* Significantly from baseline;
† Significantly different from moderate exercise intensity

Table 2.

	Exercise thresholds					
	Light		**Moderate**		**Intense**	
	Untreated	**Bretylium treated**	**Untreated**	**Bretylium treated**	**Untreated**	**Bretylium treated**
T_{es}(°C)	37.03 ± 0.05†	37.06 ± 0.04†	37.47 ± 0.05*	37.48 ± 0.05*	38.01 ± 0.07*†	38.00 ± 0.07*†
T_{sk}(°C)	32.50 ± 0.08	32.49 ± 0.09	32.52 ± 0.18	32.53 ± 0.18	32.64 ± 0.12	32.62 ± 0.11
	Post-exercise resting thresholds					
	Light		**Moderate**		**Intense**	
	Untreated	**Bretylium treated**	**Untreated**	**Bretylium treated**	**Untreated**	**Bretylium treated**
T_{es}(°C)	36.98 ± 0.06†	36.99 ± 0.07†	37.18 ± 0.04*	37.17 ± 0.04*	37.32 ± 0.06*†	37.33 ± 0.06*†
T_{sk}(°C)	36.10 ± 0.10	36.13 ± 0.07	36.22 ± 0.13	36.23 ± 0.12	36.28 ± 0.09	36.26 ± 0.12

* Significantly different from light exercise intensity;
† Significantly different from moderate exercise intensity, $p < 0.05$

Figure 1.


Cooling phase
Baseline
Rest
Treatment phase
Recovery phase
Warming phase
Local Warming
Cooling phase
Tamb: 24°C
Tsurf: 34°C
Tloc: 34°C
Tsurf: ~2°C
Tamb: 24°C
Tloc: 34°C
Tamb: 24°C
Tloc: 34°C
Tamb: 24°C
Tloc: 34°C
Tamb: 36°C
Tsurf: 48°C
Tloc: 34°C
Tamb: 24°C
Tsurf: 34°C
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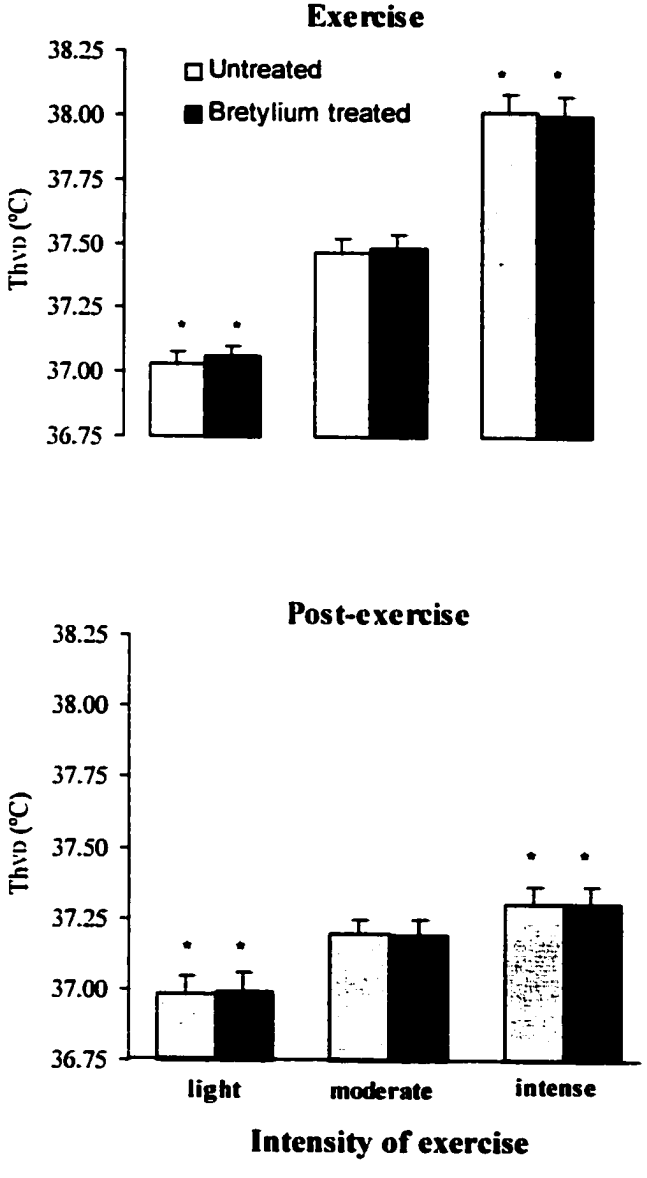
Tsurf: ~2°C
15
3
5
15
20
30-45
20-30
3
Time (min)

Figure 2.



* Indicates significant difference from moderate exercise.

CHAPTER VI

ARTICLE IV

The Effect Of Exercise Intensity On Post-Exercise Sudomotor Control

by

Julien D. Périard (B.Sc., B.Ed),

Frank Reardon (Ph.D.) and Glen Kenny (Ph.D.)

University of Ottawa, Faculty of Health Sciences,
School of Human Kinetics, Human Performance and
Environmental Medicine Research Laboratory,
Ottawa, Ontario, Canada, K1N 6N5

ABSTRACT

The purpose of this study was to evaluate the effect of exercise intensity on the esophageal temperature threshold for the onset of sweating. Esophageal temperature was monitored as an index of core temperature while sweat rate was measured using a ventilated capsule placed on the upper back. On four separate days 9 subjects (8 male and 1 female) performed 15 min treadmill running either at 55 (light), 70 (moderate) or 85% (intense) VO_2max followed by 20 min seated recovery or remained seated for 35 min (no-exercise). A liquid conditioned suit was used to increase mean skin temperature (~5.0°C/hr) until the onset of sweating occurred. In comparison with the no-exercise trial, the core temperature threshold for sweating increased significantly by 0.44, 0.68 and 1.14°C during the exercise phase and by 0.25, 0.41 and 0.57°C during the post-exercise warming phase for the light, moderate and intense exercise bouts respectively ($p<0.05$). Mean skin temperature during exercise (32.57 ± 0.13, 32.62 ± 0.08, and 32.65 ± 0.10) was significantly decreased compared to no-exercise (35.70 ± 0.12, $p<0.05$) but was not significantly different during the post-exercise warming phase. Exercise resulted in a significant increase in the threshold for sweating between moderate and intense exercise with light exercise being significantly different from the intense exercise bout ($p<0.05$). During the post-exercise warming phase, the esophageal temperature at which onset of sweating occurred was significantly increased with exercise of increasing intensity ($p<0.05$). The sweating thresholds measured were 36.97 ± 0.04, 37.13 ± 0.05, and 37.29 ± 0.05, for the light, moderate and intense respectively. These data indicate that intensity of exercise has a prolonged residual effect on the post-exercise sudomotor response by increasing the esophageal temperature at which onset of sweating occurs.

Keywords: active vasodilation, baroreceptor reflexes, heat loss, hypotension, sweating, sweat rate, thermoregulation

INTRODUCTION

Previous research from this laboratory has shown that the warm thermal response threshold for skin blood flow (SkBF) and esophageal temperature at which onset of sweating occurs are increased (~0.4°C) following dynamic exercise (17,20). More recently, it was shown that the magnitude of increase in the post-exercise resting threshold for cutaneous vasodilation (Th_{VD}) is related to the intensity of exercise (32).

Several studies have demonstrated an increase in the esophageal temperature at which onset of sweating occurs during exercise (27,28) while others have demonstrated no decrease in sweating thresholds (1,15). However, some investigations have demonstrated a reduction in the threshold for sweating (9,22) with the effect being greater as exercise intensity increases from 40 to 70% VO_2max (38).

A possible link between sudomotor and vasomotor activity has previously been observed during exercise (4,5). Recent studies have shown differences in the onset threshold and pattern of sweating and active vasodilation during exercise (11,13-15). These observations indicate that active vasodilator and sudomotor activity are governed by separate neural controls. It has been proposed that non-thermoregulatory reflexes (i.e., baroreceptor activity) modulate heat loss responses by separately modifying vasomotor and sudomotor control (12-15). However, more recent evidence has shown that non-thermoregulatory baroreflexes similarly attenuated both warm thermal response thresholds during exercise (27). Specifically, baroreceptor unloading during exercise attenuates skin blood flow and sweating suggesting a common site of interaction, proximal to the effector organ, between blood pressure and thermoregulatory reflexes (25,27).

Upright dynamic exercise is not only the source of an endogenous thermal challenge, but also stimulates an orthostatic challenge during the post-exercise phase. This latter transient effect has been previously noted and gives rise to a post-exercise, hypotensive period (3,23,24,35). Under conditions where thermal and orthostatic stress are high there is baroreceptor unloading the net effect of which is to re-establish central blood volume and arterial blood pressure. Although the exact mechanism(s) responsible for post-exercise hypotension remain undetermined, it has been shown that acute reductions in central venous pressure delay or decrease the rise in skin blood flow (26, 30) and sweating during heat stress (2,25,27,37) and possibly results in a sustained post-exercise elevation in core temperature (19). Thus it is reasonable to postulate that the post-exercise increase in the threshold for sweating is subject to significant modification by non-thermoregulatory baroreceptor reflex activity.

In a recent study, it was shown that the non-thermal baroreceptor response to post-exercise venous blood pooling by means of head-down tilt and lower body positive pressure significantly influences sudomotor activity during exercise recovery (8,18). Specifically, the modification of post-exercise venous pooling by head-down tilt results in an attenuation of the resting post-exercise elevation in the esophageal temperature at which onset of sweating occurs.

Although previous research has demonstrated an effect of exercise on post-exercise sudomotor activity, it remains to be determined if in fact exercise of increasing intensity will result in an increase in the magnitude of the post-exercise esophageal temperature for sweating. As previously indicated, recent studies suggest a post-exercise baroreceptor mediated effect on sudomotor activity similar to that observed on post-exercise skin blood flow control (8,32). Thus, in the following investigation, we studied

the effect of exercise intensity on the post-exercise esophageal temperature threshold for sweating by using three exercise intensities (55, 70 and 85% VO_2max) that are known to elicit significant differences in the post-exercise blood pressure response (33).

METHODOLOGY

Subjects

Upon approval from the Faculty of Health Sciences Human Ethics Committee, 9 healthy subjects (1 female) participated in the study after providing written, informed consent. All participants were physically active and had no history of cardiovascular or respiratory disease. Subjects (mean ± SE) were 22 ± 1 years of age, 172.11 ± 2.74 cm tall, weighed 67.72 ± 2.32 kg, had a mean aerobic capacity of 62.36 ± 2.01 ($ml \cdot kg^{-1} min^{-1}$) and a body fat of 11.06 ± 1.57 %. The female subject was eumenorrheic with regular, approximately 28-d long menstrual cycles. To control for hormonal effects the female subject was studied within 9-d after start of menstruation (follicular phase).

Instrumentation

Esophageal temperature (T_{es}) was measured using a thermocouple temperature probe inserted through a nostril, into the esophagus to the level of the heart. Skin temperature was monitored at 12 sites by Type T thermocouples integrated into heat-flow sensors (Concept Engineering, Old Saybrook, CT). The area-weighed mean skin temperature (T_{sk}) and mean heat loss (H_{sk}) were calculated by assigning the following regional percentages: head 6%, chest 9.5%, upper back 9.5%, upper arm 9%, forearm 6%, abdomen 9.5%, lower back 9.5%, anterior thigh 10%, posterior thigh 10%, anterior calf 9.5%, posterior calf 9.5%, and finger 2% (6).

Mean arterial pressure (MAP) was continuously recorded from the electrical integration of the pulsatile blood pressure signal obtained from the middle digit (Ohmeda, Finapres 2300). Mean arterial pressure was computed from the blood pressure measurements as the diastolic pressure plus one-third of the pulse pressure. Heart rate (HR) was measured using a Polar heart rate monitor (Vantage NV).

Sweat rate was measured using a ventilated capsule (≈5.0 x 3.5 cm) placed on the upper back. Anhydrous compressed air was passed through the capsule over the skin surface at a rate of 1 $l \cdot min^{-1}$ (Brooks 5850 Mass Flow Controller, Emerson Electric, Hetfield, PA). Vapor density of the effluent air was determined based on the relative humidity and temperature of the air measured by an Omega HX93 Humidity and Temperature sensor (Omega Engineering, Stanford, CT). Sweat rate was defined as the product of the difference in water content between effluent and influent air, and the flow rate. This value was adjusted for the skin surface area under the capsule and expressed in $g \cdot m^{-2} \cdot h^{-1}$.

Experimental protocol

The experimental trials were conducted in the morning at the same time of day for each subject and spaced a minimum 72-h apart. Subjects arrived following a 24-h period without heavy or prolonged physical activity, the last 12-h of which included abstinence from stimulants and alcohol, 8-h of sleep and a minimum of 0.25 l of water ingestion during each waking hour. On each study day care was taken to avoid major thermal stimuli or substantial increase of metabolic rate between awakening and the start of the experiment.

Subjects performed one incremental maximal VO_2 test on a treadmill on the first day. These data were used to select the workload for the sub-maximal experimental

exercise trials. Each subject was then required to perform a total of 4 experimental trials that were carried out in random order. On their arrival in the laboratory subjects clothed in shorts and athletic shoes were fitted with the appropriate instruments and donned a liquid conditioned suit (Three Piece Delta Temax, Pembroke, ON, Canada) covering the torso, arms and head. A schematic representation of the experimental timeline is presented in figure 1. Each of the four experimental trials began with a 15 min rest period with subjects seated in a temperature controlled chamber (24°C) during which baseline measurements were taken (baseline resting). During this time a 34°C water perfusion was started through the liquid conditioned suit by using a temperature-controlled circulation bath (Endocal, Neslab; and model 200-00, Micropump, WA). The temperate water perfusion was performed to control and stabilize skin and core temperature. Following the baseline resting phase, the liquid conditioned suit was removed. The subject then either remained seated resting (no-exercise) or exercised in an environmental chamber at 24°C (treatment phase). For the exercise treatment the subjects performed 15 min of treadmill running either at 55 (light), 70 (moderate) or 85% (intense) of their predetermined VO_2max. Immediately following these respective treatments, subjects either remained upright seated (no-exercise) or were placed similarly seated (exercise) for 20 min (post-exercise recovery phase). Subjects were donned with the liquid conditioned suit after which mean skin temperature was increased at a rate of 4.0 ± 0.6°C·hr^{-1} as the water circulating through the suit was increased to 48°C. Whole-body warming was continued until the onset threshold for sweating was noted (warming phase).

Analysis of results

The sweating threshold (Th_{sw}) was defined as the esophageal temperature measured at the onset of a sustained sweat rate exceeding 50 $g \cdot m^{-2} \cdot h^{-1}$ (22). An analysis of variance for repeated measures was used to compare esophageal temperature at the onset threshold for sweating for all four conditions (no-exercise, light, moderate and intense exercise). In the event of statistical significance ($p<0.05$), a Tukey's test was used to identify significant differences. Data are presented as means ± SE.

RESULTS

Core temperature, HR and MAP response – Treatment and Post-treatment phases

Core temperature remained stable and unchanged during the baseline period. Resting T_{es} was 36.73 ± 0.03, 36.78 ± 0.07, 36.82 ± 0.06 and 36.65 ± 0.08°C while T_{sk} 33.68 ± 0.15, 33.67 ± 0.09, 33.67 ± 0.14 and 33.68 ± 0.07°C was not significantly different between conditions and remained stable and consistent during the 15 min baseline resting period. Core temperature increased by 0.64, 0.96 and 1.61°C above baseline resting during the 55, 70 and 85% exercise bouts respectively ($p<0.05$). Exercise resulted in a post-exercise elevation of esophageal temperature of 0.3, 0.4 and 0.6°C above baseline resting for light, moderate and intense exercise bouts respectively, within the first 5 min of recovery. The temperature remained elevated for the 20 min recovery period.

Following an initial rise, heart rate levels reached a maximal plateau during the last three minutes of exercise. The end-exercise heart rates were 157.22 ± 5.04, 177.22 ±

3.63, and 189.67 ± 1.68 beats/min for the light, moderate and intense exercise trials respectively ($p<0.05$).

For all exercise conditions, post-exercise mean arterial pressure was significantly lower than baseline resting for the light, moderate and intense exercise trials respectively ($p<0.05$). These post-exercise mean arterial pressures have been reported in an earlier study (32) and showed a tendency to decrease as intensity of exercise increased from light, moderate and intense exercise (-5.89, -7.23 and -11.02 mmHg respectively). A significant difference in the post-exercise mean arterial pressure response was measured between light and intense exercise ($p<0.05$). Mean arterial pressure remained below baseline resting for the duration of the post-exercise recovery phase. All control data measurements were not significantly different from baseline following the no-exercise treatment period.

Thermoregulatory response –warming phase

Prior to the start of warming, esophageal temperature for all exercise conditions were significantly elevated above baseline. They were respectively 37.06 ± 0.07, 37.21 ± 0.06 and 37.30 ± 0.08°C for the light, moderate and intense exercise bouts ($p<0.05$). Esophageal temperature for the no-exercise trial remained unchanged at 36.74 ± 0.04. Esophageal temperature for intense exercise was significantly greater than no-exercise and light exercise ($p<0.05$). Mean skin temperatures were similar to baseline values and no differences were measured between conditions. T_{sk} for light exercise measured 34.12 ± 0.19, while moderate and intense exercise mean skin temperatures were 34.18 ± 0.23 and 34.18 ± 0.18°C respectively.

The rate of warming for the suit perfusate (~19°C·hr^{-1}) was similar for all groups and mean skin temperature was increased at the same rate of 4.0 ± 0.6 °C·hr^{-1} for all conditions. Mean skin temperatures at the onset of sweating were not significantly different between conditions. These were 35.70 ± 0.12, 35.75 ± 0.06, 35.77 ± 0.09 and 36.00 ± 0.12 °C for no-exercise, light, moderate and intense exercise.

Onset of sweating threshold

The mean esophageal temperatures at which onset of sweating occured during exercise and post-exercise are presented in figure 2. The esophageal temperature threshold for sweating during exercise was significantly elevated above control with increasing exercise intensity ($p<0.05$). Threshold values for sweating are reported for each of the respective exercise conditions in Table 2.

A pattern of increase in the onset of sweating during the post-exercise warming was noted with increasing exercise intensity. All three exercise conditions were significantly greater than no-exercise (36.97 ± 0.04, 37.13 ± 0.05, and 37.29 ± 0.05, $p<0.05$, respectively for light, moderate and intense exercise). A significant 0.16°C increase was measured between light and moderate exercise while the same significant 0.16°C increase was measured between moderate and intense exercise ($p<0.05$) indicating a marked pattern of increase with intensity of exercise.

DISCUSSION

This study was the first to investigate the effect of exercise intensity on the post-exercise thermal response for sweating. The most significant observation of this study was the increased post-exercise esophageal temperature threshold for sweating as

intensity of exercise increased. There was a 0.25, 0.41 and 0.57°C ($p<0.05$) increase in the sudomotor threshold during the post-exercise warming phase for the light, moderate and intense exercise bouts compared to the no-exercise experimental trial. Our results of an increased post-exercise core temperature threshold are consistent with previous observations of an elevated threshold for cutaneous vasodilation (36.98 ± 0.06, 37.18 ± 0.04 and 37.32 ± 0.05, $p<0.05$) following dynamic exercise at the same exercise intensities (32).

Furthermore, the core temperature threshold for sweating during exercise showed a significant elevation (0.44, 0.68 and 1.14°C, $p<0.05$) when compared to the no-exercise condition. The esophageal temperature threshold for sweating for the intense exercise trial (37.86 ± 0.16) was significantly increased from the light (37.16 ± 0.07) and moderate (37.40 ± 0.13) exercise conditions ($p<0.05$). Other studies investigating exercise have reported that although the whole body sweating response has been shown to increase with the intensity of exercise (21,31), the onset threshold for sweating is not influenced by dynamic exercise (1,15) or by exercise intensities of 25 to 60% VO_2max (29) and 75 to 200 W (39). Conversely Mekjavić and Bligh, (28) and Mack et al. (27), have observed that the threshold for sweating increases during exercise, while Jequier, (9) and Lopez et al. (22) have demonstrated a reduction in the onset threshold for sweating, with the effect being greater as exercise intensity increases from 40 to 70% VO_2max (38). Nonetheless, our current observations of an increased esophageal temperature threshold for sweating both during and following exercise indicate a possible link between vasomotor and sudomotor control of warm thermal responses.

Previous studies have suggested a linkage of sudomotor activity and active cutaneous vasodilatory activity (4,5). The eccrine sweat glands respond primarily to thermal stress through sympathetic, cholinergic stimulation. However, it has been shown that increased levels of circulating catecholamines during exercise, in particular epinephrine, facilitate thermoregulatory stimulation of eccrine sweat glands subsequent to α- and β-adrenergic receptor activation (34,36). The relative effects on sweat secretion are proportionately, 4:1:2 for cholinergic, α-adrenergic and β-adrenergic receptor stimulation respectively. It is possible that the post-exercise increase in esophageal temperature at which onset of sweating occurs (16,20) is the result of an exercise induced attenuation of cholinergic activity, however, the mechanisms remain to be elucidated. It has been suggested that activation of sweat glands by cholinergic control releases an enzyme favoring the formation of bradykinin (5) and that vasoactive intestinal polypeptide is co-released with acetylcholine from sudomotor nerves with endings on both sweat glands and cutaneous arterioles (7). This suggests a link between sweating and active vasodilation.

However, some studies indicate a dissimilarity in the onset and pattern of active vasodilation and sweating response measured during exercise which would support the hypothesis that sudomotor and active vasodilator activity are controlled by separate mechanisms (11,15). Further, that different non-thermoregulatory reflexes may act separately to modify the full expression of sweating and active vasodilatory activity (10,13). On the other hand, previous observations of a parallel increase in the post-exercise core temperature thresholds for sweating and cutaneous vasodilation would support the possibility of a thermoregulatory link between sweating and active vasodilatory response (8,20). Of significant interest was the observation that the post-

exercise increase in the thresholds for sweating and vasodilation were reversed with the application of lower body positive pressure (LBPP) (8). This observation of a parallel increase and subsequent decrease in the post-exercise warm thermal response thresholds for sweating and vasodilation following LBPP supports a linkage between cutaneous vasomotor and sudomotor activity. Although the exact mechanism responsible for the post-exercise attenuation of the sudomotor response remains to be determined, evidence from the literature does support a baroreceptor mediated response comparable to that observed with cutaneous circulation.

Bini et al. (2) previously demonstrated that changes in blood pressure may act to modulate sweat gland activity. Their observation was based on the fact that sympathetic nerve recordings from sudomotor fibers showed cardiac rhythmicity. Furthermore, studies by Mack et al. (25,27) showed a greater increase in the threshold for sweating during exercise with baroreceptor unloading. Our current observation of an increase in the post-exercise threshold for sweating in parallel with exercise of increasing intensity supports the possibility of a functional link between sweating and active vasodilatory response (27). Non-thermal baroreceptor unloading in response to increased post-exercise hypotension significantly influences cutaneous vasomotor control during exercise recovery following light, moderate and intense exercise (32). Thus, the comparable increase observed in the esophageal temperature threshold for sweating measured as a function of increasing exercise intensity, provides evidence to support the importance of non-thermal baroreflex modulation on post-exercise sudomotor control.

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TABLE LEGEND

Table 1. Mean esophageal temperature threshold for sweating for the light, moderate and intense exercise conditions. Mean skin temperature (T_{sk}); Esophageal temperature (T_{es}).

FIGURE LEGENDS

Fig. 1 Experimental protocol time line (minutes).

Fig. 2 Mean and individual resting esophageal temperature thresholds for sweating for the no-exercise, light, moderate and intense exercise conditions.

Table 1.

Exercise and post-exercise esophageal temperature thresholds for onset of sweating

	No-exercise	Light		Moderate		Intense	
	No-exercise	**Exercise**	**Post-exercise**	**Exercise**	**Post-exercise**	**Exercise**	**Post-exercise**
T_{es}(°C)	36.72 ± 0.05†	37.16 ± 0.07*	36.97 ± 0.04*†	37.40 ± 0.13*	37.13 ± 0.05*	37.86 ± 0.16*†	37.29 ± 0.05*†
T_{sk}(°C)	35.70 ± 0.12	32.57 ± 0.13*	35.75 ± 0.06	32.62 ± 0.08*	35.77 ± 0.09	32.65 ± 0.10*	36.00 ± 0.12

* Significantly different from control; † significantly different from moderate exercise.

Figure 1.

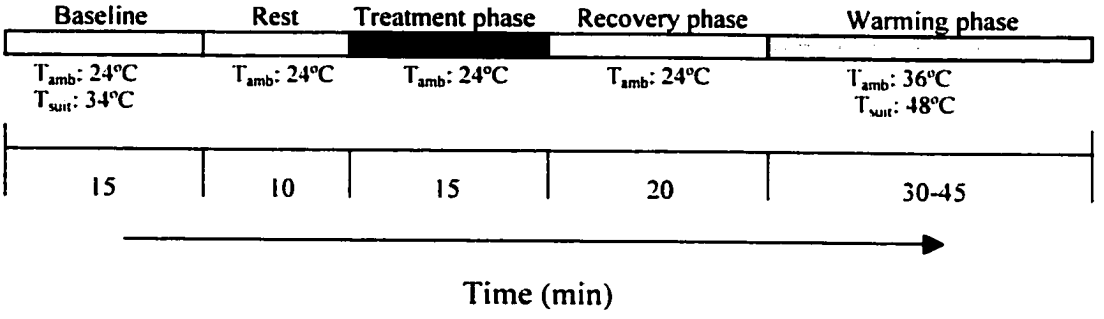
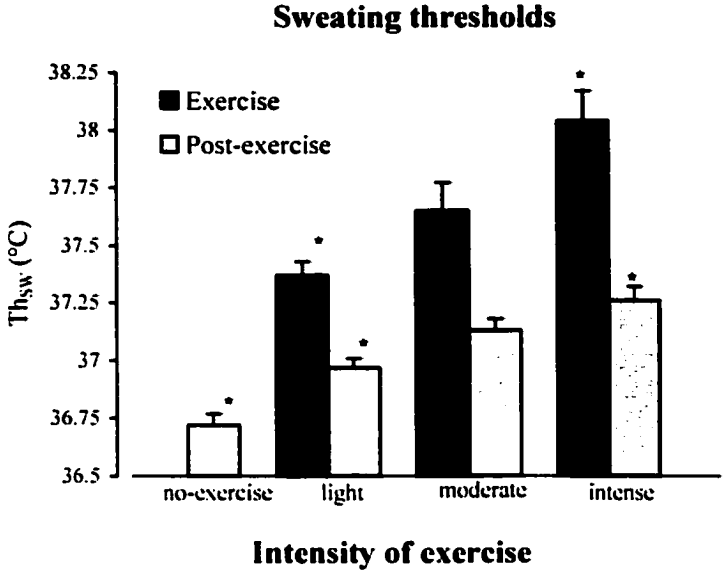

Baseline
Rest
Treatment phase
Recovery phase
Warming phase
T_{amb}: 24°C
T_{suit}: 34°C
T_{amb}: 24°C
T_{amb}: 24°C
T_{amb}: 24°C
T_{amb}: 36°C
T_{suit}: 48°C
15
10
15
20
30-45
Time (min)

Figure 2.



* Indicates significant difference from moderate exercise.

CHAPTER VI

6.0 Conclusions

An important observation from our first study examining the mechanism of post-exercise SkBF control was the similarity of response in Th_{VD} between bretylium-treated and untreated forearm sites. Based on the initial findings, it would seem that active cutaneous vasodilation plays an important role in SkBF control during whole body warming. However, unlike previous research which has shown a post-exercise increase in Th_{VD} (Kenny et al., 2000a; 2000b), the post-exercise Th_{VD} observed in our initial study was not significantly elevated (only 0.1°C) after exercise. It is noteworthy that in this case the Th_{VD} was measured ~3 hours following cessation of exercise. The fact that the Th_{VD} was no longer elevated 3-h post-exercise shows that the residual influence of exercise on the post-exercise warm thermal response of cutaneous vasodialtion is reversed within a short period.

In the second study, adjustments in protocol were necessary in order to evaluate cutaneous vasomotor response under a condition known to result in a post-exercise sustained elevation of T_{es} and Th_{VD}. In the follow up study in which the iontophoresis procedure was carried out prior to exercise, we observed a post-exercise increase in Th_{VD}. In this case, whole body warming was performed within 1 hour following cessation of exercise. Interestingly, as with the first study, a similar response in SkBF was observed at both bretylium-treated and untreated sites. In the initial study however, there was no post-exercise hypotension and no core temperature elevation was measured when the Th_{VD} was noted. On the other hand, both post-exercise hypotension and an elevated core

temperature were clearly observed during the second study indicating a possible baroreceptor modulated attenuation of active vasodilation.

Previous research has suggested that the increase in Th_{VD} is the result of a non-thermal baroreceptor mediated modulation of cutaneous circulation. The increase in Th_{VD} would therefore be manifested as an increase in vasoconstrictor activity or a decrease in active vasodilatory response. As our study showed, the similar increase in Th_{VD} for both untreated and bretylium-treated sites supports a mechanism in which a baroreceptor mediated response is manifested via a decrease in active vasodilatory response. However, the similarity in response profile for both studies (i.e., a similar response at both bretylium-treated and untreated measurement sites) may indicate that the baroreceptor mediated influence on the post-exercise warm thermal response may in fact not be the only factor involved in the increase in post-exercise Th_{VD}.

Other factors must be considered which may possibly influence the control of SkBF (i.e., vasomotor control). It has been shown that active cutaneous vasodilation is completely abolished by intradermal botulinum toxin (Kellogg et al., 1995), but is not affected by atropine. Thus active vasodilation is thought to result from the activation of a cholinergic co-transmitter system. Moreover, muscarinic blockade with atropine slightly reduces or delays vasodilator response to hyperthermia, and completely abolishes the response to exogenous acetylcholine (Kellogg et al., 1995). The failure to block vasodilation has generally been taken as an argument against the role of acetylcholine in the process. However, the partial inhibitory effect of atropine does suggest that acetylcholine plays at least a minor role. The fact that acetylcholine plays a role in active vasodilation suggests a possible involvement of nitric oxide (NO). Kellogg et al. (1998b) found that blockade of NO with L-NAME attenuates, but does not abolish,

thermoregulatory reflex-mediated cutaneous active vasodilation in humans. Thus it is possible that following exercise in which core temperature remains significantly elevated, vasomotor control via active vasodilation may be strongly influenced by both acetylcholine and nitric oxyde as the elevated core temperature returns to baseline hours after exercise (i.e., Study 1).

We were able to demonstrate that an increase in exercise intensity, is paralleled by an increase in the esophageal temperature at which onset of cutaneous vasodialtion occurs. In exercise, this increase in Th_{VD} has been associated to non-thermal baroreflex modulation of the cutaneous vascular response (Kellogg et al., 1991b; Mack et al., 2001). While it is known that exercise causes post-exercise hypotension (Coats et al., 1989, MacDonald et al., 1999; 2000), it has recently been shown that an increase in exercise intensity induces a parallel increase in the post-exercise hypotensive response and esophageal temperature elevation (Kenny and Neidre, 2002). It is thus a plausible explanation that the post-exercise hypotension associated with exercise of increasing intensity attenuated the response of active vasodilation through baroreflex modulation. However, as previously indicated, it will be necessary to conduct further studies to investigate the influence of baroreceptor activity on the post-exercise Th_{VD}. Specifically, studies involving LBPP and LBNP during which iotophoresis of bretylium is administered in order to examine the control of the cutaneous vasomotor response. Furthermore, it remains to be determined to which extent the elevation in T_{es} and post-exercise heat load influence the post-exercise skin blood flow response.

Our final observation of an increase in Th_{SW} with increasing intensity of exercise, similar to that observed with the Th_{VD}, lends support to a possible link between sudomotor and vasomotor control. It has been suggested that different non-

thermoregulatory reflexes may act separately to modify the full expression of sweating and active vasodilatory activity (Johnson, 1986; Kellogg et al., 1990). However, it has been shown that skin blood flow (Kellogg et al., 1990; Mack et al., 1998) and sudomotor activity (Mack et al., 2001; Solack et al., 1985) are subject to baroreflex modulation. Most recently, Mack et al. (2001) showed that reflex control of both sweating and active vasodilation during exercise is functionally linked and is modulated in a similar manner by baroreceptor unloading. Furthermore, sympathetic nerve recordings from sudomotor fibers show cardiac rhythmicity indicating that changes in blood pressure may act to modify sweat gland activity (Bini et al., 1980). Solack et al. (1980) showed that local sweat rate was attenuated during application of LBNP during resting. During the post-exercise recovery period, baroreceptor unloading by lower body positive pressure elicited a significant decrease in the post-exercise Th_{VD} but only a slight decrease in Th_{SW} (Jackson et al., 2000). Therefore, the extent to which baroreceptor reflexes modulate the sweating response remains to be determined. Moreover, the possibility of a functional link between vasomotor and sudomotor response suggests further study is needed.

6.1 Recommendations

In order to further isolate the contribution of baroreceptor modulation to the post-exercise cutaneous vasodilator response, a series of experiments oriented towards the effect of selective unloading of cardiopulmonary and/or carotid baroreceptors on active cutaneous vasodilation and adrenergic vasoconstriction will have to be performed. Specific studies of the sensitivity of the post-exercise thermal response to mean arterial and central venous pressure LBPP and LBNP will have to be conducted to quantify the

impact of body core heating on the interaction of mean arterial blood pressure and peripheral cutaneous blood flow.

Furthermore, study of the role of cholinergic co-transmitter activity on post-exercise active vasodilation through iontophoresis treatment of glycopyrrolate (post-ganglionic acetylcholine block) should help establish the role of acetylcholine on active vasodilatory response. Nitric oxide inhibition with the nitric oxide inhibitor N^{G}-nitro-L-argine methyl ester, will also help verify the possible role of nitric oxide in the control of post-exercsie active cutaneous vasodilation.

Finally, the post-exercise increase in the core temperature threshold for sweating may be due in part to decreased sensitivity to circulating catecholamines, post-ganglionic inhibition of sympathetic activity, or a nitric oxide dependent mechanism. Based on these observations, experiments will have to be done in conjunction with those of skin blood flow to identify the possible relationship between control mechanisms for vasomotor and sudomotor responses.

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APPENDIX A

A.1 : Physical Activity Readiness Questionnaire (Par-Q)

A.2 : Letter of information

A.3 : Informed Consent Form

Member name: _____
Telephone: h) _____ w) _____
Emergency contact name: _____
Telephone: h) _____ w) _____

workout card #: _____

A.1 : Physical Activity Readiness Questionnaire (Par-Q)

1) Your age _____
2) Are you taking medication (other than heart and blood pressure) on a regular basis? _____
3) When was the last time you exercised on a regular basis? _____
4) Do you currently have any physical limitations or an old injury than might be aggrevated by certain movements?

Physical Activity Readiness Questionnaire - PAR-Q (revised 1994)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2. Do you feel pain in your chest when you do physical activity?
☐	☐	3. In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4. Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5. Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7. Do you know of any other reason why you should not do physical activity?

If you answered

YES to one or more questions

Talk your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want - as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active - begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal - this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever - wait until you feel better; or
- if you are or may be pregnant - talk to your doctor before you start becoming more active.

Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

There is no change to my medical status: _____ year _____ initials _____ year _____ initials

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

Supported by: Health Canada / Santé Canada

I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction.

DATE _____ NAME (Please Print) _____ SIGNATURE _____

WITNESS _____

Université d'Ottawa • University of Ottawa

Faculté des sciences de la santé
École des sciences de l'activité physique

Faculty of Health Sciences
School of Human Kinetics

A.2 : Letter of information

Background information for the participant

The Effect Of Exercise Intensity On Post-Exercise Skin Blood Flow Control

Investigators:

Dr. Glen Kenny (Ph.D.), Associate Professor
University of Ottawa, School of Human Kinetics
125 University
P.O. Box 450, Station A
Ottawa, Ontario, K1N 6N5
Tel: 562-5800 x 4282

Julien D. Périard (B.Sc., B.Ed.)
University of Ottawa, School of Human Kinetics
125 University
P.O. Box 450, Station A
Ottawa, Ontario, K1N 6N5
Tel: 562-5800 x 4615

Dr. Frank Reardon (Ph.D.), Associate Professor
University of Ottawa, School of Human Kinetics
125 University
P.O. Box 450, Station A
Ottawa, Ontario, K1N 6N5
Tel: 562-5800 x 4270

Purpose

The purpose of this research is to investigate the mechanism involved in the post-exercise increase in the esophageal temperature threshold for cutaneous vasodilation at different exercise intensities. We have previously demonstrated that baroreceptor loading during acute head-down tilting and lower body positive pressure has a mediating effect on cutaneous vasomotor response. Thus it would seem that skin blood flow control during and following exercise is subject to significant modifications by non-thermoregulatory

reflexes. Modification of baroreceptor response on cutaneous vascular tone would be manifested either as an activation of sympathetic adrenergic vasoconstrictor nerves or as a withdrawal of active vasodilator activity. The following study will specifically examine the mechanism of cutaneous vasomotor response during the post exercise period for different exercise intensities.

Subject profile

Only healthy (no history of respiratory, metabolic or cardiovascular disease) male and female subjects, aged between 18 and 30 years, will be selected for the study. Participants must be physically active, that is to say exercise at least three times a week at a medium intensity for at least 20 minutes. As a subject you will be asked to participate in one preliminary session and 4 experimental sessions to be conducted on different days and separated by a minimum of 72 hours. Inclusion into the study will require a maximal oxygen consumption of at least 50 ml/kg/min, and a percent body fat under 20%.

Preliminary session

The preliminary session and experimental sessions will take place at the Laboratory for Environmental Medicine and Human Performance at the University of Ottawa. The time involvement will be approximately 2 hours for the preliminary session. During this preliminary session, all procedures will be reviewed and the experimental equipment to be used in the experiment (i.e., skin and esophageal probes, blood flow monitors, iontophoresis procedure, etc.) will be introduced. You will then be asked to complete a *Physical Activity Readiness Questionnaire (Par-Q)*. In addition, you will be asked to read and sign an *Informed consent*. Following the orientation, height and weight will be measured along with body composition by hydrostatic weighing. At the end of this session, you will be asked to perform a maximal exercise test (VO_2max) on a treadmill while oxygen consumption is measured by an automated system. During this test, you will run at a constant speed of 6 mph while the grade of the treadmill is increased by 2% every two minutes until you can no longer run at the required intensity.

Experimental sessions

Upon arrival at the laboratory (8 a.m.), you will be clothed in shorts and remain seated and rest for 30 min in order to prepare (shave and clean) and determine the most adequate area for treatment. Then iontophoresis of bretylium will be administered to one site on the ventral side of the left forearm free of any superficial veins to locally block vasoconstictor activity. The iontophoresis pad will be soaked with 180μL of the bretylium solution and iontophoresis will last 10 min at a current density of 0.4 mA for a total current density of 400 $\mu A/cm^2$. A second site without iontophoresis will serve as a control site. One hour after iontophoresis, you will be seated in a climatically controlled chamber (26°C), instrumented appropriately and dress in a liquid conditioned suit. The liquid conditioned suit will control your skin temperature at 34°C by circulating water through the garment covering the entire body except the feet, hands, face and left forearm. The special laser-Doppler probe holders will control local temperature at measurement sites at 34°C throughout the experiment to ensure that skin blood flow changes are due to reflex rather then local mechanisms. Data collection will then begin with a 15 min normothermic baseline period followed by a 3 min cooling strategy where the water perfusing the suit will rapidly be lowered to ~2°C. After verification of blockade you will

remove to liquid conditioned suit and perform, in random order and on separate days, four experiments on a treadmill corresponding to control (no exercise), or 55, 70 and 85% of your VO_2max. Following the exercise trial, you will once again dress in the liquid conditioned suit and remain seated and rest for 20 min. Whole body warming will then be applied by circulating warm water (48°C) through the perfusion garment and elevating ambient temperature to 36°C. Whole body warming will be terminated when a clear threshold for vasodiation is established (30-45 min, T_{sk} ~38°C). Once the threshold for vasodilation has clearly been established at both the treated and untreated sites, the water circulating through the liquid conditioned suit will return to 34°C and ambient temperature will return to 24°C. Local warming will then begin by increasing the temperature of the probe holders to 43°C in order to determine your peak cutaneous vascular conductance. A final cooling strategy will be administered ~30 min after the start of local warming with the probes remaining at 43°C.

Please note that you will be asked to abstain from alcohol, spiced foods, stimulants and severe or prolonged physical activities for at least 12 hours prior to all sessions. It is highly recommended that you avoid eating before the trial. You are asked to ensure that you are properly hydrated by drinking at least 100 ml every waking hour prior to the experimental trial.

Esophageal probe: In order to monitor central body temperature, a flexible esophageal temperature probe (2 mm in diameter) will be inserted through one of your nostrils, while you 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 soon passes.

Iontophoresis: The measurement is specific to skin, and does not produce any residual effect beyond that expected on the selected skin surface sites (i.e., abolition of vasoconstrictor response). The depth of measurement is ~ 1 mm^2. Iontophoresis is a drug delivery technique whereby charged molecules are delivered into the skin, or even systematically, by means of a direct current. Very high levels of bretylium have toxic effects on gastrointestinal smooth muscle and cardiac muscle. However, as measurement is controlled by a constant current delivery system, there are minimal risks associated with this procedure, and possible discomforts are slight tingling specific to the site of measurement upon absorption of the bretylium.

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 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 during the habituation, recovery and whole body warming periods. Blood pressure will be monitored continuously by a Finapres fingertip blood pressure monitor. You will feel a slight pressure on your finger.

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

Oxygen consumption: An automated metabolic cart (Medgraphics Cardiopulmonary Diagnostic 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 preliminary session only.

Laser-Doppler flowmetry: Forearm skin blood flow will be assessed at two adjacent sites with a laser-Doppler flow probe on the midanterior forearm. The laser-Doppler flow sensor will be placed through a probe holder and taped to the cleaned skin surface at a location that gives a consistent reading. The laser-Doppler probe holders will be used to control local skin temperature at the measurement sites throughout the experiment. Local warming and temperature measurement will be accomplished through heating elements and thermocouples embedded within the probe holders. This measuring device does not result in any discomfort or residual medical effects.

Risks and discomforts

You should be aware that there are some minor physical risks associated with any form of exercise. There is essentially no major risk for young, healthy, active people while performing sub-maximal exercises. Some effects of maximal exercise testing are nausea, dizziness, fainting, abnormal blood pressure, chest pain and leg cramps. 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. You 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.

Perforation of the esophagus, or oral or nasal cavities can occur during insertion of the esophageal probe (potentially causing inflammation and infection). However, such an incident is very rare and no such incident has ever occurred in this laboratory and we are unaware of any such occurrences. The risk of transmission of infectious disease is negligible as each subject has his own sterile probe that will be disposed of once all tests have been completed. There is also some risk of skin irritation and rash associated with the taping of the skin probes and iontophoresis treatment.

There are also certain risks that accompany a mark elevation in core temperature. These include: headache, extreme weakness, dizziness, nausea, hyperventilation,

hypotension, confusion, diarrhoea, vomiting and loss of consciousness. These risks will, however, be minimized by terminating the exercise or heat stress test at the first sign of distress and cooling the individual immediately.

Anonymity and Confidentiality

Anonymity is ensured throughout all aspects of this research study. All data will be presented in pooled form and all raw data will be stored under alphanumeric codes in computer memory. Access to the data is restricted to the investigators. You are encouraged to request and discuss the results of the experimental trials at any time. The results of the preliminary session (body composition and VO_2max test) will be available to the participant upon completion of the study.

For the entire duration of the four testing days, it is fully understood that you may refuse to participate or withdraw from the study at any time, without question or prejudice.

Once you have read this information, please feel free to ask any questions. In order to confirm that you understand and have read all of the above information, please sign below.

Volunteering Participant: _____ Date: _____

Signature of Researcher: _____ Date: _____

If you have any questions regarding the conduct of this study, please feel free to contact Dr. Kenny at 562-5800 ext 4282 or Julien Périard at 562-5800 ext 4615.

Any information requests or complaints about the ethical conduct of this research project may be addressed to the Health Sciences and Science Research Ethics Board by contacting Catherine Lesage.

Catherine Lesage
Protocol officer for ethics in research
30 Stewart Street, room 301
University of Ottawa
Ottawa, ON K1N 6N5
(613) 562-5387
clesage@uottawa.ca

Université d'Ottawa • University of Ottawa

Faculté des sciences de la santé
École des sciences de l'activité physique

Faculty of Health Sciences
School of Human Kinetics

A.3 : Informed Consent Form

INFORMED CONSENT OF THE PARTICIPANT

Research involving human subjects requires written consent of the participants. I, _____, hereby volunteer to participate as a subject in the study entitled **"The Effect Of Exercise Intensity On Post-Exercise Skin Blood Flow Control"**. I have read the information presented in the background information package and have had the opportunity to ask questions to the investigators I understand that the purpose of this research is to investigate the mechanism involved in the post-exercise increase in the esophageal temperature threshold for cutaneous vasodilation for different exercise intensities. As a participant, I will be exposed to some risks associated with exercise, as well as with the experimental equipment and consider these risks acceptable. Also, I acknowledge that my participation in this study, or indeed any research, may involve risks that are currently unforeseen. I understand and accept these risks.

I have filled out a "Par-Q and You: Physical Activity Readiness Questionnaire". I understand that I will be asked to participate in one preliminary session and 4 experimental sessions. During the preliminary sessions, I will be asked to perform a maximal exercise test on the treadmill, as well as have my body composition evaluated by means of hydrostatic weighing. This preliminary session should last approximately 2 hours. During the 4 experimental trials I will be instrumented with physiological devices after which I will be required to wear a nylon liquid conditioned suit, all described in the background information sheet. I understand that I will be required to perform one incremental maximal VO_2 test on a treadmill. These data will be used to select the workload for the sub-maximal experimental trial. I understand that I will be required to participate in four experimental sessions on separate days separated by a minimum of 72 hours. During the experimental trials I will be required to either: a) run on a treadmill at either 55, 70 or 85% of my pre-determined peak oxygen consumption (VO_2max) for 15 min, or b) stand on the tredmill for 15 min in a climatically controlled chamber (26°C ambient temperature). Before the exercise or no-exercise sessions I will receive selective abolition of the adrenergic vasocontrictor response in the skin of my left forearm by local iontophoresis of bretylium treatment. Following each treatment condition, I will be required to remain seated and resting for 20 min. With the use of the liquid conditioned suit, my skin temperature will be lowered for ~3 min. The exercise condition will follow the cooling. Then warm water will be circulated through the suit until such time as I begin sweating and vasodilating. Local skin at the treatment sites will then be raised to 43°C for approximately 30 min in order to determine maximal cutaneous vascular conductance.

125, rue Université C.P. 450, Succ. A
Ottawa (Ontario) K1N 6N5 Canada

125 University St., P.O. Box 450, Stn. A
Ottawa, Ontario K1N 6N5 Canada

(613) 562-5852 • Téléc./Fax (613) 562-5149

The total duration of each experimental session should be around 4 hours, including the instrumentation period. I understand that in order to evaluate skin blood flow response, the investigators will apply a chemical procedure referred to as iontophoresis of bretylium on a 1.13 cm^2 site on my forearm. Also, my central body temperature (esophageal), skin temperature, sweat rate, heart rate, skin blood flow, and blood pressure will be measured during the experimental trials.

I have been informed that I should abstain from alcohol, stimulants, spiced foods and severe physical activities for at least 12-h prior to the tests, and from any food before the test. I understand that I should ingest approximately 100 ml of water every waking hour prior to the experimental trial.

I understand that the anonymity of my data will be maintained at all times. The data will be presented in pooled form and identified by a specific code. I will not be identified in any written reports or publications. Access to the data will be restricted to the principal investigators and no records bearing my name will leave the institution.

I recognize that there will be no direct benefit to me from my participation in this study (besides receiving a fitness evaluation). However, the investigators will be able to learn more about temperature regulation during and following exercise in humans. At the end of the study, the investigators will be able to share the results with me (including the results of the preliminary evaluation), if I so desire.

I am aware that I am free to refuse to participate and may withdraw my consent without prejudice or questions at any time. I know that I can ask questions before, during or after the various tests.

I have been given a copy of this consent form, as well as the background information for me to keep.

Signature of participant: _____ Date: _____

Signature of Researcher: _____ Date: _____

APPENDIX B

B.1 : Certification of Institutional Human Research Ethics Committee

Université d'Ottawa · University of Ottawa

Cabinet du vice-recteur à la recherche
Office of the Vice-Rector, Research

B.1 : Certification of Institutional Human Research Ethics Committee

Glen Kenny
School of Human Kinetics
Montpetit Hall
Intra

January 23, 2002

Dear professor Kenny:

You will find enclosed the Health Sciences and Science Research Ethics Board renewal certification for your research project *Thermoregulation research (File H01-02-C).*

Please note that it is the responsibility of researchers to:

a) Send a copy of this approval to the Research Services, if necessary;
b) Notify the ethics office of any changes in the research project;
c) Fill out an annual status report to be sent to the Protocol officer for ethics in research. Such report can be found on the ethics web site at: http://www.uottawa.ca/ethics/REB

Sincerely yours,

Lise Frigault
Education officer for ethics in research
30 Stewart Street, room 301

550, rue Cumberland
Ottawa (Ontario) K1N 6N5 Canada

550 Cumberland Street
Ottawa, Ontario K1N 6N5 Canada

(613) 562-5270 • Téléc./Fax (613) 562-5271

Université d'Ottawa · University of Ottawa

Faculté des sciences de la santé
Cabinet du doyen

Faculty of Health Sciences
Office of the Dean

May 6, 1998

Professor Glen Kenny
School of Human Kinetics
Faculty of Health Sciences
125 University, Montpetit Hall
INTRA

Dear Professor:

Subject: **Your project entitled --**
"Thermoregulation Research"

It is my pleasure to inform you that the Faculty of Health Sciences, Human Research Ethics Committee, after study of the documentation provided, concluded that your project met the appropriate standards of ethical acceptability and falls within **CATEGORY 1A.**

I hereby attach a copy of the certificate of clearance granted by the University Human Research Ethics Committee.

This certificate is valid for a period of one year from the time of issuance. I would also like to remind you that, in accordance with the policies of the UHREC, it is your responsibility to notify the Committee of any major changes in this project.

On behalf of the Committee, I wish you success in your project.

Sincerely,

J. Roger Proulx, Ph.D.
Chair, Human Research Ethics Committee

Encl.

451, ch. Smyth
Ottawa (Ontario) K1H 8M5 Canada

451 Smyth Rd.
Ottawa, Ontario K1H 8M5 Canada

(613) 562-5432 • Telec./Fax (613) 562-5437

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Faculté des sciences de la santé
Cabinet de la doyenne
Faculty of Health Sciences
Office of the Dean

CERTIFICATION OF INSTITUTIONAL HUMAN RESEARCH ETHICS COMMITTEE FACULTY OF HEALTH SCIENCES

This is to certify that the Institutional Human Research Ethics Review Committee of the Faculty of Health Sciences has examined the research proposal **from Professor Glen Kenny from the School of Human Kinetics** for the project ***"Thermoregulation Research"*** and concludes that, in all respects, the proposed research protocol meets the appropriate standards of ethical acceptability, at a **Category 1A** level.

MEMBERS OF THE COMMITTEE

Name (Optional)	Position held	Department of discipline
Victor Boucher	Professor	Audiology and Speech-Pathology Program
François Tremblay	Professor	Physiotherapy Program
Claire-Jehanne Dubouloz	Professor	Occupational Therapy Program
Jocelyne Tourigny	Professor	School of Nursing
Julian Roberts	Professor	Department of Criminology
Roch Paquin	Member-at-Large	
Mark Grenier	Student	School of Human Kinetics
J. Roger Proulx	Chair	Human Research Ethics Committee School of Human Kinetics

SIGNATURE

03/05/98 — **Date**

Committee Chairperson - J. Roger Proulx, Ph.D.

451, ch. Smyth
Ottawa (Ontario) K1H 8M5 Canada
451 Smyth Rd.
Ottawa, Ontario K1H 8M5 Canada
(613) 562-5432 • Telec./Fax (613) 562-5437

APPENDIX C

C.1 : Testing Procedure for the Predicted Mmaximal Oxygen Consumption Test

C.2 : Testing Procedure for the Hydrostatic Weighing Test

C.3 : Experimental Protocol for Pilot Study

C.1 : Testing Procedure for the Predicted Mmaximal Oxygen Consumption Test

VO_2max – Treadmill

Name:
Weight:
Height:
Age:
Occupation:

Temperature:
Humidity:
Pressure:
Gender:

Time (min)	Speed (mph)	Incline (%)	Heart rate (bpm)
0-2	6	2	
2-4	6	4	
4-6	6	6	
6-8	6	8	
8-10	6	10	
10-12	6	12	
12-14	6	14	
14-16	6	16	
16-18	6	18	
18-20	6	20	
20-22	6	22	

VO_2max breath by breath: ml/Kg/min
VO_2max 30 sec average: ml/Kg/min
VO_2max: l/min

Comments:

C.2 : Testing Procedure for the Hydrostatic Weighing Test

Hydrostatic Weighing

Name:
Weight:
Height:
Age:
Occupation:

Temperature:
Humidity:
Pressure:
Gender:

Water temperature:
Water density:
Gastro intestinal volume: 0.1 l

Weight in water (Kg)	Total weight in water (Kg)	Weight of the chair (Kg)

Body fat % (Siri):					

Comments:

C.3 : Experimental Protocol for Pilot Study

Methodology for pilot studies

The first iontophoresis procedure developped in our laboratory followed the protocol developed by Mack et al. (2001). A team from the University of Ottawa was sent to the John B. Pierce Laboratory and Department of Epidemiology and Public Health, Yale School of Medicine in New Haven Connecticut. Due to differences in technical equipement and instrumentaion, the initial protocols failed to render effective adrenergic blockade. Subsequent trials were conducted evaluating other established protocols (Kellogg et al., 1989; Mack et al., 2001; Thomas et al., 1999) with the purpose of developing a protocol that would generate consistent α_1-adrenergic vasoconstrictor blockade. The following section describes the protocol developed as a part of these studies.

Initial experimental timeline

First, subjects arrived at the laboratory and were instrumented appropriately with skin temperature and heat flux disks, an esophageal temperature probe and heart rate monitor. Baseline measurements were then taken for 30 min while subjects remained seated in a climatically controlled chamber (27°C). Following the baseline period, they either performed 15 min of cycle ergometer exercise at 75% of maximal capacity or no exercise sitting on the cycle ergometer. Upon completion of either condition, subjects donned a liquid conditionned suit that covered the entire body except the face, hands, feet and left forearm. At this point, two treatment sites were defined on the ventral side of the left forearm. The sites covered hair follicules in order for the solution to be better absorbed. One treatement site was infused with bretylium. Once the drug was delivered

the subjects sat upright in the chamber for 120-m to allow for teatment to take effect. Fifteen minutes before the end of the treatment period, installation of the blood pressure device was done on the right hand. Following the treatment period, subjects were cooled for 3-m with 2°C water circulating through the liquid conditionned suit. After a 10 min recovery period, passive heating (T_{amb} = 36°C) with the liquid conditionned suit (T_{suit} = 48°C) began until clear thresholds for vasodilation and sweating occured. Subjects were then allowed to recover for 30 min when a second cooling strategy was applied to verify the effectiveness of the drug.

Iontophoresis procedure modifications to experimental protocols

A number of different treatment conditions were evaluated for the iontophoresis procedure. As listed below, the concentration of the solution, current density and number of treatment sites were manipulated according to different litterature procedures in order to determine an effective protocol.

1) Solution : 100 mM
Current density 10 min at 0.4 mA
Number of sites : 1

2) Solution : 100 mM
Current density 15 min at 0.3 mA
Number of sites : 2

3) Solution : 100 mM
Current density of site one : 15 min at 0.3 mA, site two : 20 min at 0.4 mA
Number of sites : 2

4) Solution : 100 mM
Current density 20 min at 0.4 mA
Number of sites : 2

5) Solution : 100 mM
Current density 20 min at 0.4 mA, plus 10 min at 0.3 mA
Number of sites : 1

6) Solution : 100 mM
Current density 10 min at 0.4 mA
Number of sites : 1 with local heating at 34°C and shaved treatment site

7) Solution : 10 mM
Current density 10 min at 0.4 mA
Number of sites : 1 with local heating at 34°C and shaved treatment site

Pilot study : interpretation of technical difficulties

Based on the results from the pilot work, the following were noted to have a negative effect on the succesful blockade of α_1-adrenergic vasoconstrictor tone :

- not shaving the treatment site;
- baseline period to long;
- not locally warming the sites throughout the experiment;
- using high concentrations of bretylium and possibly saturating the treatment sites;
- delivering the drug after exercise;
- waiting period to long before start of initial cooling and warming losing optimal period for post-exercise response observation; and,
- recovering 30 min after warming before the second cooling.

Based on our findings it was determined that the following procedures should be included as part of the protocol in order to ensure successful treatment of iontophoresis of bretylium :

- shaving of treatment area;
- local warming of treated and untreated sites, keeping local temperature constant;
- starting experimental trials with iontophoresis and exercising after treament effect;
- using a 10 mM for only 10 min; and,
  waiting only 60 min to start experiment after drug delivery.