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Differences in the Post-exercise Threshold for Cutaneous Vasodilation Between Men and Women

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DIFFERENCES IN THE POSTEXERCISE THRESHOLD FOR CUTANEOUS VASODILATION BETWEEN MEN AND WOMEN

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THESIS

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ABSTRACT

Recent studies, primarily in males, have shown that postexercise cutaneous vasodilation is attenuated by baroreceptor unloading subsequent to lower body venous pooling. However, gender differences in the control of cutaneous circulation may exist given that females appear to show a reduced tolerance to orthostatic challenge and, an attenuated responsiveness in mechanisms that regulate arterial pressure. We evaluated the hypothesis that females would demonstrate a greater reduction in postexercise mean arterial pressure (MAP) and concurrently a greater increase in the postexercise core temperature at which onset of cutaneous vasodilation occurred as compared to males. Fourteen subjects (7 males and 7 females) of similar age and fitness status remained seated resting for 15 min or cycled for 15 min at 70% of peak oxygen consumption followed by 15 min of seated recovery. A liquid conditioned suit was used to increase mean skin temperature, while local forearm temperature was clamped at 34°C. Cutaneous vascular conductance was calculated using the ratio of laser-Doppler flow from the forearm and MAP. Skin blood flow was measured continuously at two forearm skin sites, one with (untreated) and without (treated with bretylium tosylate) intact α-adrenergic vasoconstrictor activity. No gender differences in heart rate or core temperature were measured at the end of either exercise or the no-exercise resting trials. Core temperatures were similar to baseline values prior to the start of whole-body warming. Postexercise HR remained significantly elevated by +16 and +19 beats/min above baseline rest for the male and females respectively. MAP was significantly reduced from baseline rest by -9 and -14 mmHg for the male and females respectively. A greater decrease in the postexercise MAP was noted in females ($P<0.05$). No differences in core temperature,

HR and MAP were measured in the no-exercise trial. The postexercise threshold for cutaneous vasodilation was significantly elevated above no-exercise resting by 0.21°C and 0.37°C for the males and females respectively as measured at the untreated site. A similar increase of 0.19°C and 0.39°C was measured for the males and females respectively at the treated site. A larger difference in the magnitude of the thresholds was measured for females as compared to the males ($P<0.05$). There were no gender differences in the sensitivity (slope). These observations support our hypothesis that females would demonstrate a greater reduction in MAP concurrent with a greater increase in the postexercise threshold for cutaneous vasodilation as compared to males. The primary mechanism of control for the gender difference in postexercise skin blood flow is likely the result of an altered active vasodilatory response and not an increase in adrenergic vasoconstrictor tone.

Keywords: cutaneous vascular conductance, postexercise hypotension, baroreceptors, thermoregulation, heat loss.

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CHAPTER I

INTRODUCTION

1.1 Introduction

Despite the well-characterized cardiovascular and thermoregulatory responses to rest and exercise, there remains a lack of information on the integrated responses of these reflexes during exercise recovery. In a resting individual, the response of skin blood flow to heat stress is characterized by an internal temperature threshold, beyond which the rise in skin blood flow is fairly steep. However, studies have shown that skin blood flow can be compromised during the postexercise period as a result of altered hemodynamics, where dynamic exercise has been shown to induce a residual effect on thermal control resulting in an increase of approximately 0.3-0.4°C in the postexercise core temperature at which cutaneous vasodilation occurs (Jackson and Kenny, 2003; Kenny, Jackson and Reardon, 2000; Kenny, Periard, Journeay, Sigal and Reardon, 2003).

This postexercise increase in the threshold for cutaneous vasodilation is consistent with a baroreceptor-mediated attenuation of postexercise skin blood flow, subsequent to lower body venous pooling (Jackson and Kenny, 2003). During upright inactive recovery from dynamic exercise, venous pooling in the previously active musculature results in reduced cardiac filling and postexercise arterial hypotension. As a result, the baroreceptors are unloaded, subsequently stimulating vasoconstriction and a restoration of postexercise mean arterial pressure. These findings are supported by other studies demonstrating that a reversal in lower body venous pooling, postexercise hypotension and thus baroreceptor unloading by head down tilt (Kenny et al., 2000) and lower body positive pressure (Jackson and Kenny, 2003) application, results in an attenuation of the

resting postexercise elevation in the esophageal temperature for cutaneous vasodilation. Further evidence that the attenuation of the postexercise heat loss responses of skin blood flow is related to nonthermal cardiovascular adjustments associated with blood pressure regulation includes the observation that an increase in the postexercise hypotensive response, induced by exercise of increasing intensity, results in a relative increase in the onset threshold for cutaneous vasodilation (Kenny et al., 2003).

While the preceding observations have predominantly been conducted using male participants, there is a paucity of information concerning the cardiovascular and thermoregulatory responses of women during the postexercise period. Males and females differ in their response to physiological stressors and it remains to be determined how potential differences in the postexercise cardiovascular response between the genders may influence control of the cutaneous circulation.

It has been observed that women have a lower tolerance to various orthostatic challenges at rest (Gotshall, Tsai and Frey, 1991; White, Gotshall and Tucker, 1996) including a greater susceptibility to postexercise hypotension when compared to men (Carter, Watenpaugh and Smith, 2001). For example, during upright inactive recovery from dynamic exercise women exhibit significantly greater decreases in mean arterial pressure compared to men and therefore, are at increased risk of postexercise orthostatic hypotension (Carter et al., 2001). It has been suggested that the mechanisms that contribute to such differences include women regulating blood pressure via different mechanisms (Carter et al., 2001), less responsiveness in mechanisms that regulate changes in arterial pressure (Gotshall, Aten and Yumikura, 1994; Convertino, 1998; Gotshall, 2000; Carter et al., 2001), impaired baroreflex function (convertino, 1998),

greater venous compliance and pooling of blood and lesser blood volume (Fu, Arbab-Zadeh, Perhonen, Zhang, Zuckerman, and Levine, 2004).

If the postexercise increase in the threshold for cutaneous vasodilation is the result of a baroreceptor-mediated attenuation of postexercise skin blood flow and women demonstrate a greater hypotensive response during the postexercise period, then women may respond with a greater increase in the postexercise onset threshold for cutaneous vasodilation compared to men. To date there have been no studies that have examined the gender differences in the postexercise threshold for cutaneous vasodilation.

The baroreceptor-mediated response of skin blood flow can be due to either less active vasodilator activity or enhanced adrenergic vasoconstrictor activity (Kellogg, Johnson and Kosiba, 1990). These two mechanisms can be studied separately by the iontophoretic application of bretylium tosylate, which blocks neurally mediated adrenergic vasoconstriction without modification of active vasodilation. The cutaneous vasodilator system is subject to nonthermoregulatory baroreflex modulation (Kellogg et al., 1990). During resting heat stress baroreceptor unloading modulates skin blood flow by causing a withdrawal of active cutaneous vasodilation (Kellogg et al., 1990). Kenny et al. (2003) examined the mechanism of skin blood flow control during the postexercise period in men and concluded that the reflex activity associated with the postexercise increase in the threshold for vasodilation is also likely mediated through an alteration in active vasodilator activity rather than through activation of sympathetic vasoconstrictor activity. Unclear is whether this increase in the onset threshold for cutaneous vasodilation in women will involve a change in active vasodilator or adrenergic vasoconstrictor control of skin blood flow. Therefore, this investigation will also address this question.

1.2 Rationale

There is increasing evidence that the attenuation of the postexercise heat loss response of skin blood flow is related to nonthermal cardiovascular adjustments associated with blood pressure regulation. For example, the application of lower body positive pressure and head down tilt following exercise were shown to increase stroke volume and mean arterial pressure and reverse the postexercise increase in the onset threshold for cutaneous vasodilation (Jackson and Kenny, 2003; Kenny et al., 2000). Furthermore, an increase in the postexercise hypotensive response, induced by exercise of increasing intensity, was shown to result in a relative increase in the onset threshold for cutaneous vasodilation (Kenny et al., 2003).

The studies examining postexercise control of skin blood flow have primarily been conducted on male subjects and thus the possible gender differences in the postexercise threshold for vasodilation have not been quantified. Of interest is that there is increasing evidence of females demonstrating a greater postexercise hypotensive response compared to males (Carter et al., 2001). This observation along with the finding that greater increases in the postexercise hypotensive response, induced by exercise of increasing intensity, results in a relative increase in the onset threshold for cutaneous vasodilation in males, it is possible that females will demonstrate a greater reduction in mean arterial pressure following exercise concurrent with a greater increase in the postexercise threshold for cutaneous vasodilation as compared to males.

The effect of this baroreceptor response on cutaneous vascular tone can manifest either as an alteration of active vasodilator outflow or as an activation of sympathetic vasoconstrictor activity (Kellogg et al., 1990). During resting heat stress with

baroreceptor unloading (lower body negative pressure), as well as during the postexercise hypotensive period, also thought to result in baroreceptor unloading, the reflex activity associated with the increase in the threshold for vasodilation is mediated through an alteration in active vasodilator activity rather than through activation of sympathetic vasoconstrictor activity (Kenny et al., 2003; Kellogg at al., 1990). Therefore, an additional purpose for this study is to determine if this increase in the threshold for cutaneous vasodilation in women will also involve a decrease in active vasodilator activity as opposed to an increase in sympathetic vasoconstrictor activity. This investigation will allow us to reveal gender differences in the postexercise onset threshold for cutaneous vasodilation, a fundamental response necessary for appropriate thermoregulation, as well as possible differences in the mechanism of skin blood flow control during this period.

1.3 Objectives

(1) To examine the different responses between men and women in the postexercise esophageal temperature threshold for forearm cutaneous vasodilation.

(2) To determine if the shift in cutaneous vasodilation in women involves inhibition of active vasodilator activity as in men, or activation of sympathetic vasoconstrictor activity.

1.4 Hypothesis

(1) It is hypothesized that females will demonstrate a greater reduction in mean arterial pressure following exercise and concurrently a greater increase in the postexercise esophageal temperature at which onset of cutaneous vasodilation occurs as compared to males.

(2) It is hypothesized that the increase in the onset threshold for cutaneous vasodilation in females will manifest as altered active vasodilator activity rather than activation of adrenergic vasoconstrictor tone.

1.5 Significance

Most investigations have focused on the integration of the cardiovascular and thermoregulatory systems at rest and during exercise, with very few directing their attention to the postexercise recovery period. Skin blood flow is an important means by which heat is dissipated from the body during the postexercise period. Dynamic exercise can result in altered hemodynamics and consequently compromised thermoregulatory function that may persist into the postexercise period contributing to syncope, orthostatic intolerance or postexertional heat related illnesses. Furthermore, most investigations that have focused on the postexercise period have based their research on male responses and it is difficult to extrapolate these findings to women. Thus, this study will complement the information already acquired regarding the integrated response between the cardiovascular and thermoregulatory reflexes on the postexercise resting threshold for cutaneous vasodilation. It will also provide additional insight into possible differences in

the postexercise esophageal temperature threshold for vasodilation between men and women as well as any differences in the mechanism of skin blood flow control.

1.6 Limitations and Delimitations

- The results of this experiment will not be generalized to the entire population, as the volunteers being studied are young, healthy, physically active males and females from the University of Ottawa with no known health problems.
- On average, men and women in our society differ from each other with respect to morphological, behavioral, fitness and hormonal variables. However, in this investigation we will match men and women for these variables. Thermal and cardiovascular differences between the sexes are negligible when these variables are controlled for, therefore, our laboratory findings may be applied only to those who also match the characteristics of those in our investigation.
- This experiment will not study the possible menstrual cycle phase effects within women on the postexercise integrated response of both the thermoregulatory and cardiovascular system.
- Many variables could possibly influence skin blood flow, including those of central command, baroreceptors, metaboreceptors and thermoreceptors. Work by Kenny and colleagues (Jackson and Kenny, 2003; Kenny et al., 2000; Kenny et al., 2000) have demonstrated that the post exercise increase in the threshold for cutaneous vasodilation is associated with a baroreceptor mediated attenuation of post exercise skin blood flow. Therefore, while we investigate the gender differences in the resting postexercise threshold for cutaneous vasodilation, we

will not be able to reveal which variable (i.e. baroreceptor reflexes) may be mediating such changes.

- Hydration status of our subjects will not be verified during the experiment. Studies have shown that hypohydration increases the threshold for cutaneous vasodilation (Fortney, Wenger, Bove, and Nadel, 1984).
- It has already been established that during the postexercise period there is pooling of blood in the previously active musculature as well as increased venous pooling (Piepoli, Isea, Pannarale, Adamopoulos, Sleight and Coats, 1993). This study will not directly measure muscle blood flow and therefore any conclusions made regarding the pooling of blood in the postexercise period will be speculative.
- With the use of Bretylium Tosylate we will be able to observe the neurogenic reflexes associated with the postexercise threshold for cutaneous vasodilation, however, this method will not allow us to examine locally released substances that may also work to mediate vasodilation.

CHAPTER II

REVIEW OF LITERATURE

2.1 Baroreceptor control of blood pressure

Blood pressure is influenced by alterations in cardiac output, peripheral resistance and/or blood volume; however, the cardiovascular system has neural and chemical controls in place to ensure that mean arterial pressure is maintained at adequate levels. An important negative feedback control mechanism that provides immediate short-term control of changes in blood pressure involves baroreceptors and the baroreflex.

There are pressure sensitive arterial baroreceptors, which are located in the aortic arch and carotid sinus, and cardiopulmonary baroreceptors, which are located in the atria, ventricle and pulmonary vessels (Berne and Levy, 2001). Baroreceptors are mechanoreceptors that essentially respond to stretch rather than pressure, where for example a rise in pressure causes arterial distention, which in turn excites the mechanoreceptors.

When blood pressure increases and stretches the baroreceptors (baroreceptor loading), afferent impulses from the arterial and cardiopulmonary baroreceptors to the nucleus tractus solitarius in the medulla (cardiovascular center) stimulate parasympathetic nerves and inhibit sympathetic nerve impulses. This results in a reduced heart rate and a decrease in vasoconstrictor tone, in turn leading to vasodilation and thus, a decrease in blood pressure (Johnson, 1986). On the other hand a decline in blood pressure (baroreceptor unloading) initiates vasoconstriction and an increase in heart rate, causing blood pressure to rise (Johnson, 1986).

Mean arterial pressure is altered when stimuli alter total peripheral resistance and/or cardiac output. For example, during exercise parasympathetic withdrawal and progressive sympathetic stimulation activate dilation in the active musculature and constriction in non-exercising tissues. This in conjunction with an increase in cardiac output increases the individual's mean arterial blood pressure. Baroreceptors continually monitor cardiac filling and adjust sympathetic stimulation to exercising skeletal muscles to increase or decrease vascular resistance to maintain blood pressure (Levick, 2000). Baroreceptor modulation of blood pressure is also critical during the postexercise period, as will be evident later in this review.

2.2 Thermoregulation

During thermoneutral conditions, internal body temperature is regulated at approximately 37°C $\pm$ 1°C through the balance between heat loss and heat production. The body continually produces heat during resting conditions and heat loss adjusts to match heat production to maintain body heat balance and core temperature equilibrium. When the rate of heat production exceeds the rate of heat loss or vice versa, there is a change in body heat content, which in the end results in changes in core temperature (Webb, 1995).

A negative feedback control system allows the body to adjust to changes in factors that can affect body heat balance, such as air temperature, humidity, air movement, metabolism and body movement in order to avoid an imbalance in temperature homeostasis (Stephenson and Kolka, 1993). The preoptic region of the anterior hypothalamus is the main integrating center that continually stimulates changes

in thermoregulatory effector responses when there are deviations in the body's heat balance. The hypothalamus is activated by means of afferent input from peripheral and central thermal receptors, as well as by changes in blood temperature perfusing the area. The hypothalamus responds to the input by initiating heat loss or heat production through autonomic effector pathways, thus restoring heat balance (Jacobs, Martineau and Vallerand, 1994).

When heat is gained from exercise and/or the environment causing an increase in core temperature, the hypothalamus stimulates an increase in the rate at which heat must be dissipated to the environment in order to keep body heat content and thus, core temperature from rising to dangerous levels (Stephenson and Kolka, 1993). Heat-dissipating responses include decreased metabolism, sweating and increases in skin blood flow (Gisolfi and Wenger, 1984) so that heat can be exchanged with the environment via radiation, evaporation and conduction, while convection enhances the latter two.

2.3 Heat dissipation

The evaporation of sweat and cutaneous vasodilation are two essential components for thermoregulation in humans (Shibasaki, Kondo and Crandall, 2003). Since increased skin blood flow is a major heat dissipating mechanism the interaction between the thermoregulatory and cardiovascular system is important and the ability to effectively thermoregulate would be limited if the cardiovascular system was not functioning adequately.

The transition from rest to exercise results in an increase in metabolic heat production in the muscle, while heat dissipating mechanisms react more slowly. The

body's cardiovascular system increases blood flow to the active muscles to meet metabolic demands (Stephenson and Kolka, 1993). The increased blood flow to the active musculature also transports the heat from the muscle to the body's core, thus increasing core temperature. When core temperature is elevated, sympathetic nerves activate the sweat glands and affect dilation of the skin vasculature to dissipate heat to the environment via conduction, radiation and evaporation (Stephenson and Kolka, 1993). The following two sections will focus on these two essential thermoregulatory components; sweating and skin blood flow.

2.3.1 Sweating

As thermogenesis exceeds thermolysis, there is an increase in core temperature and the release of acetylcholine from sudomotor nerves stimulates the eccrine sweat glands and sweat rate is increased within several seconds. Such increases in sweating are a result of the density of activated sweat glands, the increase in sweat output per gland or both combined (Kondo, Shibasaki, Aoki, Koga, Inoue and Crandall, 2001).

During passive heating at rest the main stimulus for sweating is thought to be thermal in origin. In addition to thermal (i.e., internal and skin temperatures) modulation of sweating, non-thermoregulatory mechanisms are also thought to contribute to the sweating response during exercise (Shibasaki et al., 2003), although their contribution remains unclear. A review by Shibasaki and colleagues (2003) suggests that central command and the stimulation of muscle metaboreceptors could affect the sweating response during exercise. On the other hand, the contribution of muscle mechanoreceptor stimulation and the affect of baroreceptor unloading on sweating require additional investigation because of inconsistent results (Shibasaki et al., 2003).

2.3.2 Skin blood flow

Cutaneous circulation is principally mediated by reflex activity. The surface of the skin is divided into acral (hands, feet, nose, lips and ears) and non-acral (head, limbs and trunk) regions according to control. Reflex control of the cutaneous circulation involves both sympathetic active vasoconstrictor and active vasodilatory systems. Control of skin blood flow, and thus heat flow, in the acral regions is thought to be mediated by adrenergic vasoconstrictor nervous activity; while that of the non-acral regions is mediated by both an adrenergic vasoconstrictor system and a sympathetic vasodilator system of unknown neurotransmitter co-released with acetylcholine (Kellogg, Johnson and Kosiba, 1989; Kenny and Johnson, 1992; Kellogg, Pergola, Piest, Kosiba, Crandall, Grossmann and Johnson, 1995).

The vasoconstrictor system is tonically active in thermoneutral environments. When there are slight changes in daily activity or ambient temperature, minor changes in the activity of this system is responsible for the maintenance of normal body temperature (Pergola, Kellogg, Johnson and Kosiba, 1994). On the other hand, during heat stress in resting conditions skin blood flow is influenced by a core temperature threshold, above which there is a sharp rise in skin blood flow (Johnson, 1986). The rise in core temperature is the thermoregulatory drive that stimulates temperature sensitive neurons in the central nervous system, ultimately affecting skin blood flow. In this case, up to 70 percent of cardiac output can be redirected to cutaneous circulation in order to dissipate heat, compared to the 5-10 percent received during thermoneutral conditions (Rowell, 1974). The primary mechanism for increasing skin blood flow during heat stress is via activation of the active vasodilator system (Rowell, 1986), while withdrawal of the

vasoconstrictor system is responsible for 10-20% of the resulting cutaneous vasodilation (Pergola et al., 1994).

Along with reflex control, the local temperature of an area of skin is a powerful factor that also contributes to the control of skin blood flow at that particular site. Local warming of the skin causes a localized vasodilation that increases with local temperature and a sustained local temperature of 42°C for 20-40 minutes can elicit maximal cutaneous vasodilation in that area (Pergola, Kellogg, Johnson, Kosiba and Solomon, 1993; Kellogg, Liu, Kosiba, and O'Donnell, 1999). The usual response to such local warming begins with an initial rapid increase in blood flow during the first few minutes that relies primarily on local activity of sensory nerves. This is followed by a slight decrease in skin blood flow and then a slower increase in vasodilation that reaches a plateau that is initiated and maintained primarily by nitric oxide (Pergola et al., 1993; Kellogg et al., 1999). Thus, directly heating the skin can activate neurogenic reflexes and locally released substances, however, the interaction between the local factors and the neural mechanisms involved in the vasodilator response are poorly understood (Minson, Berry and Joyner, 2001).

2.4 Nonthermoregulatory control of skin blood flow

During exercise there is both a thermoregulatory and nonthermoregulatory reflex role in the control of skin blood flow. The thermoregulatory drive for cutaneous vasodilation during exercise is the same as seen at rest, thus, providing a stimulus for vasodilation to promote heat transfer from the core to the body's surface for evaporative heat loss (Kenny and Johnson, 1992). However, there are two nonthermoregulatory

effects of exercise that help to redistribute blood flow to working muscles to meet metabolic demands, a circumstance that may ultimately reduce one's ability to dissipate heat. First, there is an initial vasoconstriction at the onset of exercise to redistribute blood flow from inactive to active muscle, which has been shown to act through the adrenergic vasoconstrictor system (Kellogg, Johnson and Kosiba, 1991). Second, there is an elevated core temperature threshold for cutaneous vasodilation, which has been shown to be the result of a delay in the activation of the active vasodilatory system (Kellogg et al., 1991; Kenny and Johnson, 1992). Therefore, circulatory regulation appears to take precedence over temperature regulation, negatively affecting heat dissipation (Gisolfi and Wenger, 1984).

Along with the reflexes associated with exercise, baroreceptor mediated reflexes also compete with thermoregulatory reflexes to affect cutaneous circulation. These main pressure receptors can alter cutaneous vasodilation while carrying out their role in the regulation of heart rate and blood pressure. As discussed above, these pressure receptors monitor the degree of stretch that a vessel undergoes as a result of changing blood pressure. With increased blood pressure these receptors are stimulated leading to vasodilation and inhibition of vasoconstriction, while a decrease in baroreceptor stimulation from a decrease in blood pressure leads to the opposite response.

Under resting conditions, baroreceptor unloading by means of lower body negative pressure or upright tilting has been shown to modulate skin blood flow (Crandall, Johnson, Kosiba and Kellogg, 1996; Kellogg et al., 1990). For example, Kellogg et al. (1990) showed that during resting heat stress, 3 minutes of –40 mmHg lower body negative pressure resulted in significant reductions in cutaneous vascular

conductance. They also demonstrated that during resting heat stress, the reduction in cutaneous vascular conductance from baroreceptor unloading was due to withdrawal of cutaneous vasodilation.

Baroreflex control of skin blood flow during exercise has also been examined. Mack, Cordero and Peters (2001) demonstrated that baroreceptor unloading by application of -40 mmHg lower body negative pressure during exercise delayed the onset of skin blood flow. Baroreceptor unloading limited cutaneous vasodilation during exercise and was reversed after the removal of the blood pressure challenge. This response in the skin was due primarily to withdrawal of active cutaneous vasodilator drive. Therefore, the cutaneous vascular system is clearly subject to nonthermoregulatory baroreflex modulation both at rest and during exercise (Kellogg et al., 1990; Mack et al., 2001). The nonthermoregulatory baroreceptor influence on skin blood flow during the postexercise period will be addressed later in this review.

2.5 Postexercise Thermal Response

It is well known that at rest and during exercise the body has the capacity to continually alter its heat producing and heat loss mechanisms to maintain core temperature or prevent it from increasing to dangerous levels. Dynamic exercise provides a thermal challenge to the body and one would think that in the resting post exercise recovery period, in absence of heat production from exercise, there would be a rapid return of core temperature to baseline levels to avoid the possible development of heat related illness. However, investigations prove contrary to this notion.

Following dynamic exercise there is a prolonged (~60min) elevation in postexercise esophageal temperature (~0.5°C) compared to pre exercise resting levels that is directly related to the intensity of exercise (Kenny and Neidre, 2002). This elevation in post exercise core temperature is not the result of an increase in oxygen consumption, as oxygen consumption has been shown to rapidly return to pre exercise levels following exercise (Kenny, Giesbrecht and Thoden, 1996). First of all, it has been suggested that there is a persistent peripheral vasodilation in the previously active musculature following exercise causing pooling of warmed blood, thus confining the heat of the previously active muscle and increasing muscle heat content (Piepoli et al., 1993).

Additionally, recent studies have indicated that exercise induces a residual effect on thermoregulatory control mechanisms, resulting in an increase of 0.3-0.6°C in the postexercise resting esophageal temperature threshold (relative to no exercise resting) at which cutaneous vasodilation and sweating occur (Kenny et al., 2003; Kenny et al., 2000; Kenny et al., 1996). A postexercise increase in the threshold for heat dissipating mechanisms can assist in the overall decrease in the rate of heat loss (i.e., decrease in thermosensitivity) and increase in core temperature recovery time seen postexercise. Kenny and Neidre (2002) explain that this increase in threshold in combination with the trapping of warm blood and elevated muscle heat load could result in a time-dependent transfer of the heat from muscle to the core during the postexercise period, resulting in the prolonged elevation in esophageal temperature.

Investigations reveal that the effect of exercise on the postexercise resting threshold for warm thermal responses (cutaneous vasodilation and sweating) and subsequent prolonged elevation of postexercise core temperature (Kenny and Neidre,

2002; Kenny, Denis, Boule, Proulx, Thoden and Reardon, 1999; Kenny, Giesbrecht, Jette, Reardon and Thoden, 1997; Thoden, Kenny, Reardon, Jette and Livingstone, 1994) is likely influenced by an exercise induced alteration in hemodynamics seen during recovery. The possible impact of cardiovascular reflexes on the postexercise resting threshold for warm thermal responses will be considered later in this review.

2.6 Gender Differences in Thermoregulation

Female physiology (i.e. sex hormones), anthropometric characteristics (i.e. body mass, body size), body composition (i.e. lean body mass, body fat content), and social behavior (i.e. acclimation, daily physical activity) are factors that can contribute to differences in thermal response between men and women (Kaciuba-Uscilko and Grucza, 2001). However, once men and women are matched for these variables most gender related thermoregulatory differences disappear, making it important to consider these factors when undertaking a study that will include thermoregulatory responses.

2.6.1 Morphological considerations

Although men and women do not always differ from a morphological perspective, the generally observed differences in body size and composition between them can make a difference in their thermoregulatory response. First, women on average have a smaller total body mass resulting in a larger surface area-to-mass ratio. Second, women generally have a greater percentage of their body mass as fat compared to men (Anderson, 1999; Tarnopolski, 1999; Kaciuba-Uscilko and Grucza, 2001). With a greater surface for evaporative cooling, less metabolically active tissue to generate heat and a larger peripheral heat sink, an individual may be at an advantage when subject to heat stress. On

the other hand, disadvantages may include a greater amount of fatty tissue being carried by the muscles and a lower thermal conductivity of fatty tissues compared to other tissues (Anderson, 1999). However, adiposity, body surface area, body mass and the surface to mass ratio contribute only partly to the thermal response to exercise, while the individuals' maximal aerobic capacity also has an influence. On average, women achieve a lower maximal oxygen uptake compared with men due to the greater muscle mass, hemoglobin concentration, heart size and volume, stroke volume and cardiac output generally seen in men (Tarnopolski, 1999).

Men and women respond to deviations in core temperature in a similar manner and when they are matched for age and acclimation and body size related variables are adjusted for individual maximal oxygen uptake, most gender related thermoregulatory differences disappear, with the exception of differences in sweating (Kaciuba-Uscilko and Grucza, 2001). Sweating begins at a higher core and skin temperature in women compared to men; therefore, more heat is stored before evaporative cooling begins (Burse, 1979; Tarnopolski, 1999). During exposure to heat, sweating is also substantially slower and less intensive in women compared to men despite a greater density of activated sweat glands (Kaciuba-Uscilko and Grucza, 2001).

2.6.2 Sex hormones

A second major factor that plays a role in modulating thermoregulation is the female reproductive cycle, making it important to control for menstrual cycle phase in thermoregulatory studies. Both estrogen and progesterone appear to influence body temperature and skin blood flow control in women (Charkoudian, Stephens, Pirkle, Kosiba and Johnson, 1999; Charkoudian and Johnson, 1997). It is well established that

resting core temperature is increased in women during the luteal phase of the menstrual cycle when progesterone and estrogen are elevated, compared to the follicular phase when these hormones are low (Hessemer and Bruck, 1985; Stephenson and Kolka, 1985). Estrogen has been shown to promote cutaneous vasodilation and thus heat dissipation, while the influence of progesterone is less clear, and is thought to possibly inhibit cutaneous vasodilation (Charkoudian and Johnson, 2000). Therefore, the menstrual cycle related changes in core temperature are thought to be primarily effects of progesterone (Charkoudian, 2003). In response to high levels of estrogen and progesterone the reflex thermoregulatory control of the cutaneous vasoconstrictor system has shown to be shifted to higher core temperatures (Charkoudian and Johnson, 1999).

The response of cutaneous circulation at rest and during exercise is also modified according to the phase of the menstrual cycle. At rest and during exercise, the onset threshold for cutaneous vasodilation is shifted to a higher core temperature (+0.3-0.5°C) in the luteal phase of the menstrual cycle compared with the follicular phase. Charkoudian and Johnson (1997) showed that this shift in threshold with elevated reproductive hormones is due to a shift in control of the active vasodilator system, thus a delay in the initiation of active vasodilation specifically to a higher core temperature. However, it remains unclear whether these reproductive hormones act directly on a central and/or peripheral level to alter thermoregulatory responses to heat stress and exercise (Brooks, Morgan, Pierzga, Wladkoeski, O'Gorman Derr and Kenney, 1997).

During exercise as well as in the postexercise period, studies show that the onset threshold for cutaneous vasodilation acting to dissipate heat is elevated when compared to the control response at rest in a thermoneutral environment. The core temperature

threshold for cutaneous vasodilation during exercise has been shown to be higher in women than in men; however, menstrual cycle phase was not controlled for in these studies (Cunningham, Stolwijk and Wenger, 1978; Roberts, Wenger, Stolwijk and Nadel, 1977). In a study by Kolka, Stephenson, Rock and Gonzalez (1987) no differences were observed between men and women in either the onset core temperature threshold or the slope of skin blood flow to core temperature during exercise and moderate heat stress when the women were studied in their follicular phase and the men and women were matched for training history. Core temperature is also similar between men and women who are tested in the follicular phase (low estrogen and progesterone levels) of their menstrual cycle (Kaciuba-Uscilko and Grucza, 2001).

Morphological, behavioral and hormonal differences within and between men and women can clearly affect thermoregulation. Therefore, if both men and women comprise a study population, it appears essential that women be studied in the follicular phase to avoid the influence of the sex hormones. It is also important to control for morphological, behavioral and fitness variables in thermoregulatory studies to avoid their influence and ensure a more uniform comparison (Tarnopolsky, 1999).

2.7 Cardiovascular Response to Inactive Recovery from Exercise

While much of the cardiovascular alterations at rest and during exercise have been documented repeatedly, little research has focused on the cardiovascular response during recovery from exercise, even though this period is associated with increased risk of syncope (Carter et al., 2001).

During inactive recovery from dynamic exercise there is an observed drop in mean arterial pressure thought to be due to differences in the recovery of the two determinants of arterial pressure. Stroke volume and cardiac output decline from their high exercise values much more rapidly than the increase in systemic vascular resistance, resulting in post exercise hypotension (Halliwill, 2001). The persistent systemic vasodilation following exercise in addition to the absence of the skeletal muscle pump during inactive recovery is said to contribute to the increase in venous pooling (Carter, Watenpaugh, Wasmund, Wasmund and Smith, 1999; Kilgour, Gariepy and Rehel, 1993). The subsequent reduction in central venous pressure and cardiac filling pressure (preload) results in a higher heart rate when compared to pre exercise resting values. In addition, stroke volume is maintained due to a decrease in afterload and increase in cardiac contractility (Halliwill, 2001), which results in an increase in cardiac output when compared to resting levels before exercise (Kilgour et al., 1993).

2.8 Gender Differences in Cardiovascular Response to Orthostatic Challenges

Orthostatic intolerance is characterized by compromised venous return to the heart, which leads to diminished stroke volume, cardiac output and often a fall in mean arterial pressure. In order to maintain blood pressure, the baroreceptor reflex system increases heart rate, cardiac contractility and vasoconstriction (Frey and Hoffler, 1988). Several studies have shown that in comparison to men, women are more susceptible to orthostatic intolerance (Convertino, 1998; Gotshall et al., 1991; Gotshall et al., 1994; Shoemaker, Hogeman, Khan, Kimmerly and Sinoway, 2001; White et al., 1996) and possibly have less responsiveness in mechanisms that work to regulate the subsequent

decrease in mean arterial blood pressure (Convertino, 1998; Gotshall et al., 1994; Shoemaker et al., 2001).

When examining the gender differences in response to the application of lower body negative pressure, Frey and Hoffler (1988) observed that men experienced greater increases in peripheral resistance while women experienced greater increases in heart rate. Therefore, they suggested that women might respond to orthostatic challenges with greater vagal withdrawal, whereas sympathetic stimulation to the peripheral vasculature is the primary response for men (Frey and Hoffler, 1988). Other studies have observed greater heart rate increases in women compared with men during lower body negative pressure (Montgomery, Kirk, Payne, Guber, Newton and Williams, 1977; White et al., 1996; Frey, Mathes and Hoffler, 1986). Furthermore, investigations have also been able to support the hypothesis that men respond to orthostatic challenges with greater sympathetic stimulation to the vasculature (Frey et al., 1986; Gotshall et al., 1991; Gotshall et al., 1994).

Upright inactive recovery from exercise is characterized by a hypotensive period as a result of venous pooling in the previously active musculature and subsequent reduction in stroke volume. Such an orthostatic challenge engages the cardiovascular reflex system to maintain blood pressure. To our knowledge, only one study has examined the cardiovascular responses of both men and women during complete inactive recovery from dynamic exercise. In a study by Carter et al. (2001) the hemodynamic responses in men and women were compared during active and inactive recovery from 3 minutes of dynamic exercise. This investigation demonstrated that during upright inactive recovery from exercise women had a greater decrease in mean arterial pressure compared

to men. Following exercise, women had a faster return of stroke volume and cardiac output to pre-exercise levels, suggesting a greater decrease in venous return and thus greater peripheral pooling compared to men (Carter et al., 2001). During the short 5 minute period when comparisons were made, women did not produce the same degree of compensatory vasoconstriction as did the men and experienced less of an increase in total peripheral resistance (Carter et al., 2001). Additionally, heart rate in women was not significantly higher than that of males during inactive recovery, all of which contributed to the significantly lower mean arterial pressure observed in women compared with the men during this period.

A number of mechanisms have been put forth in an attempt to explain the lower tolerance to various orthostatic challenges and the greater susceptibility to postexercise orthostatic hypotension in women when compared to men. For example, as discussed above it has been suggested that it may be the result of females regulating blood pressure via different mechanisms (Carter et al., 2001; Senitko, Charkoudian and Halliwill, 2002) or that females may have an attenuated responsiveness in the mechanisms that regulate arterial pressure (Convertino, 1998; Gotshall, 2000). Moreover there is evidence both for and against the involvement of such factors as increased venous compliance of the lower extremeties, greater pooling of blood in the pelvic area, reduced blood volume (Convertino, 1998) and impaired baroreflex function (Christou, Jones, Jordan, Diedrich, Robertson and Seals, 2005). However, it is reasonable to suspect that differences in orthostatic intolerance between men and women are associated with differences in some or all of these mechanisms.

2.9 Integrated postexercise thermoregulatory and cardiovascular response

Research has only recently begun to focus on the interaction between thermoregulatory and cardiovascular reflexes and the integrated response postexercise. Following submaximal exercise studies have shown a prolonged post exercise elevation in esophageal temperature that is greater in magnitude with increasing exercise intensity and increasing post exercise hypotension (Kenny and Niedre, 2002). As discussed above, these investigators suggested that the sustained post exercise elevation in esophageal temperature is due to a combination of the residual heat load of the previously active muscle and the reduced skin blood flow and sweating observed during inactive recovery. Post exercise peripheral vasodilation is thought to cause a pooling of warm blood, thus, trapping heat in the muscle, which may then be gradually transferred to the core resulting in a sustained post exercise elevation in esophageal temperature (Kenny and Niedre, 2002).

The increase in venous pooling and skin blood flow immediately following exercise decreases total peripheral resistance and thus, central venous pressure. The decrease in filling pressure of the heart results in a baroreceptor mediated reduction in skin blood flow to increase total peripheral resistance (Kenny and Niedre, 2002; Kilgour et al., 1993). Studies have specifically shown an increase in the core temperature threshold at which cutaneous vasodilation begins, which ultimately has the ability to compromise post exercise temperature regulation (Jackson and Kenny, 2003; Kenny et al., 2000; Kenny et al., 2000). This nonthermal cardiovascular reflex may have an influence on the overall decrease in the rate of heat loss and associated increase in the postexercise core temperature recovery time.

Following exercise systolic pressure falls below pre-exercise levels resulting in what is known as post exercise hypotension, which is thought to be due to venous pooling in the visceral organs and/or lower limb extremities (Halliwill, 2001). Venous pooling reduces central blood volume and cardiac filling pressure, thus lowering systemic arterial blood pressure causing baroreceptor unloading. The modification of post exercise venous pooling by head down tilt (Kenny et al., 2000) and lower body positive pressure (Jackson and Kenny, 2003) results in an attenuation of the resting post exercise elevation in the esophageal threshold temperature for cutaneous vasodilation and aids in whole body heat loss (Jackson and Kenny, 2003). Therefore, it has been suggested that the post exercise increase in the threshold for cutaneous vasodilation (attenuation of skin blood flow) is a consequence of baroreceptor unloading, via lower body venous pooling (Kenny et al., 2003).

An increase in the postexercise hypotensive response, induced by exercise of increasing intensity, has been shown to result in a relative increase in the onset threshold for cutaneous vasodilation, an overall decrease in the rate of heat loss and an associated increase in the postexercise core temperature recovery time (Kenny et al., 2003). This is significant since women have a greater decrease in mean arterial pressure during the postexercise period compared to men (Carter et al., 2001), leading to the possibility of a greater increase in the postexercise onset threshold for cutaneous vasodilation in women. Altered control of skin blood flow in females during exercise recovery may result in a decreased ability to dissipate heat.

CHAPTER III

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CHAPTER IV

ARTICLE

Differences in the postexercise threshold for cutaneous active vasodilation between men and women

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ABSTRACT

Recent studies, primarily in males, have shown that postexercise cutaneous vasodilation is attenuated by baroreceptor unloading subsequent to lower body venous pooling. However, gender differences in the control of cutaneous circulation may exist given that females appear to show a reduced tolerance to orthostatic challenge and, an attenuated responsiveness in mechanisms that regulate arterial pressure. We evaluated the hypothesis that females would demonstrate a greater reduction in postexercise mean arterial pressure (MAP) and concurrently a greater increase in the postexercise core temperature at which onset of cutaneous vasodilation occurred as compared to males. Fourteen subjects (7 males and 7 females) of similar age and fitness status remained seated resting for 15 min or cycled for 15 min at 70% of peak oxygen consumption followed by 15 min of seated recovery. A liquid conditioned suit was used to increase mean skin temperature, while local forearm temperature was clamped at 34°C. Cutaneous vascular conductance was calculated using the ratio of laser-Doppler flow from the forearm and MAP. Skin blood flow was measured continuously at two forearm skin sites, one with (untreated) and without (treated with bretylium tosylate) intact α-adrenergic vasoconstrictor activity. No gender differences in heart rate or core temperature were measured at the end of either exercise or the no-exercise resting trials. Core temperatures were similar to baseline values prior to the start of whole-body warming. Postexercise HR remained significantly elevated by +16 and +19 beats/min above baseline rest for the male and females respectively. MAP was significantly reduced from baseline rest by -9 and -14 mmHg for the male and females respectively. A greater decrease in the postexercise MAP was noted in females ($P<0.05$). No differences in core temperature,

HR and MAP were measured in the no-exercise trial. The postexercise threshold for cutaneous vasodilation was significantly elevated above no-exercise resting by 0.21°C and 0.37°C for the males and females respectively as measured at the untreated site. A similar increase of 0.19°C and 0.39°C was measured for the males and females respectively at the treated site. A larger difference in the magnitude of the thresholds was measured for females as compared to the males ($P<0.05$). There were no gender differences in the sensitivity (slope). These observations support our hypothesis that females would demonstrate a greater reduction in MAP concurrent with a greater increase in the postexercise threshold for cutaneous vasodilation as compared to males. The primary mechanism of control for the gender difference in postexercise skin blood flow is likely the result of an altered active vasodilatory response and not an increase in adrenergic vasoconstrictor tone.

Keywords: cutaneous vascular conductance, postexercise hypotension, baroreceptors, thermoregulation, heat loss.

INTRODUCTION

It is well documented that recovery from dynamic exercise results in significant cardiovascular and thermoregulatory perturbations (27, 45). Following cessation of exercise, there are profound changes in the mechanisms that regulate and determine mean arterial pressure which result in hypotension that is both vascular and neural in origin (5, 24, 31). The magnitude of this decrease in mean arterial pressure is more pronounced and more enduring subsequent to exercise of increasing intensity (9). Postexercise hypotension is thought to occur in part as a result of venous pooling in the previously active musculature (5, 27, 37, 45). Such pooling of blood in the lower extremities tends to reduce cardiac filling and unload baroreceptors (15).

It is well documented that the active vasodilator control of cutaneous circulation is the primary mechanism for increasing skin blood flow during heat stress. Studies have shown that the cutaneous vasodilatory system is subject to nonthermoregulatory baroreflex modulation (20, 33). Furthermore, acute reductions in cardiac filling delay or decrease the rise in skin blood flow (33). Of note, the same factors that give rise to these cardiovascular phenomena postexercise as described above, have been shown also to be responsible for the attenuation of heat loss postexercise (17, 18, 25). Specifically, exercise has been shown to result in a residual increase in the onset threshold for skin blood flow (25) and sweating (26) and concomitant decrease in the rate of core temperature decay (16, 17). There is increasing evidence that the attenuation of the postexercise heat loss responses of skin blood flow and sweating is related to nonthermal cardiovascular adjustments associated with blood pressure regulation. For example, an increase in the postexercise hypotensive response, induced by exercise of increasing

intensity, was shown to result in a relative increase in the onset threshold for cutaneous vasodilation (25). Further, changes in hemodynamic response induced by the application of lower body positive pressure in the upright position postexercise, such as an increase in stroke volume and mean arterial pressure, were shown to reverse the postexercise increase in the onset threshold for cutaneous vasodilation (16).

The studies examining postexercise control of cutaneous circulation have primarily been conducted in male subjects. To date, it remains to be determined how possible gender differences in the postexercise cardiovascular response may influence control of the cutaneous circulation. The study of gender differences in the control of cutaneous circulation is particularly important when one considers that there is increasing evidence demonstrating differences in postexercise blood pressure regulation in females as compared to males in the upright seated position. Carter et al. (2) measured a greater reduction in mean arterial pressure in females as compared to males at 5 min following a 3-min exercise bout. Fisher et al. (8) demonstrated a comparable gender response in postexercise resting mean arterial pressure measured over the course of a 90-min recovery following 35-min of cycling at 60% $\dot{V}O_{2peak}$. In addition, Senitko et al. (39) showed a gender difference in postexercise mean arterial pressure response in the upright position in sedentary individuals. These differences may possibly be explained by the observations that females have a reduced tolerance to orthostatic challenges at rest (6, 12, 13, 40, 44), and/or an attenuated responsiveness in mechanisms that regulate arterial pressure (6, 13).

Thus, the purpose of this study was to examine the gender differences in the threshold for active cutaneous vasodilation using an exercise paradigm which has

previously been shown to elicit postexercise hypotension in males (24, 25). Specifically we tested the hypothesis that females would demonstrate a greater reduction in mean arterial pressure and concurrently a greater increase in the postexercise core temperature at which onset of cutaneous vasodilation occurred as compared to males. Further, we hypothesized that an increase in the onset threshold for cutaneous vasodilation would likely manifest as altered active vasodilator activity rather than activation of adrenergic vasoconstrictor tone.

METHODS

Subjects

Fourteen healthy and physically active subjects (7 males and 7 females) volunteered and gave written consent to participate in this study, previously approved by the Research Ethics Board of the University of Ottawa. The female subjects were eumenorrheic with regular, approximately 28-d long menstrual cycles. To control for hormonal effects, the female subjects were tested during the early follicular phase (1-5 days after the onset of menstruation) of their menstrual cycle.

Five to seven days before the experiments, body adiposity and peak oxygen consumption ($\dot{V}O_{2peak}$) were estimated respectively using total body densitometry and a progressive cycling protocol performed on a Monark cycle ergometer. The $\dot{V}O_{2peak}$ value was used to select the submaximal workload (~70 % $\dot{V}O_{2peak}$) for the experimental exercise phase of the study. $\dot{V}O_{2peak}$ expressed per kg of FFM was calculated for all subjects. The physical characteristics of the subjects are presented in Table 1.

Instrumentation

Esophageal temperature was monitored with a Mon-a-therm esophageal thermocouple (Mon-a-therm®, Mallinckrodt Medical, St-Louis, MO) inserted through a nostril and positioned at the level of the heart, at a depth equivalent to about ¼ of the individual's standing height placing the tip of the thermocouple at the level of the left atrium (35). Skin temperature was monitored at 12 sites by heat-flow sensors with integrated skin temperature sensors (Concept Engineering, Old Saybrook, CT, model FR-025-TH44018-6). The area-weighted mean skin temperature 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%.

Oxygen consumption was measured using an automated metabolic analyzer (MedGraphics, St-Paul, MN, USA). Mean arterial pressure was calculated from the electrical integration of the pulsatile blood pressure signal obtained non-invasively, from the middle digit of the left hand (Ohmeda, Finapres 2300) referenced at the third intercostal space. The Finapres system is based on the volume clamp method first introduced by Penaz. These blood pressure data were recorded (with the Finapres servo control on) and stored continuously at 5 s intervals. Heart rate was monitored using a Polar coded transmitter, recorded continuously and stored with a Polar Advantage interface and Polar Precision Performance software (Polar Electro Oy, Finland).

Skin blood flow was measured by laser-Doppler velocimetry (PeriFlux System 5000, Main control unit; PF5010 LDPM, Function unit; Perimed AB, Stockholm, Sweden) from the left mid-anterior forearm. The laser-Doppler flow probes (PR 401

Angled Probe, Perimed AB, Stockholm, Sweden) were taped to cleaned skin on the ventral aspect of the forearm, in an area that was not overly vascular to visual inspection and from where consistent readings were noted. Cutaneous vascular conductance was calculated throughout the experimental protocol using the ratio of 30-s averages of laser-Doppler flux and mean arterial pressure.

In order to determine the effect of exercise on cutaneous active vasodilator activity postexercise, the vasoconstrictor activity effect was abolished by iontophoretic application of bretylium tosylate (21) to 1.0 cm^2 of skin on the ventral side of the left forearm. Bretylium tosylate blocks the presynaptic release of neurotransmitters from sympathetic adrenergic nerve endings within the area of application. Thus neurally mediated adrenergic vasoconstriction is selectively blocked without modification of active vasodilation (21). A Perilont Micropharmacology System PF480-1 (Perimed AB, Stockholm, Sweden) was used in all experimental trials for the application of bretylium tosylate by iontophoresis. The system uses a disposable drug delivery electrode (PF 481-1) in which a 10mM solution of bretylium tosylate in propylene glycol is delivered. The protocol consisted of a 10-min application period at a current density of 400 $\mu A/cm^2$ (21). In all experiments, skin blood flow was measured simultaneously at both an untreated and bretylium-treated site. At such site, a servo-heater controlled laser-Doppler flow probe was mounted on the skin. Local skin temperature at the probe holder was maintained at 34°C throughout the experimental protocol.

The effectiveness of the vasoconstrictor system blockade was tested prior to, and following the experimental protocol by cooling the entire skin surface (except feet, hands,

face and the local skin site on the forearm) using a liquid conditioned suit (Med-Eng, Ottawa, ON, Canada) and recording the skin blood flow and mean arterial pressure.

Core and skin temperature, and skin blood flow were recorded (Hewlett Packard, data-acquisition module, model 3497A), stored (Hewlett Packard, model PC-312, 9000) and displayed in real time continuously at 10 s intervals.

Experimental protocol

Each subject performed a total of 2 experimental trials carried out in random order. Twelve (6 females and 6 males) of the 14 subjects performed their experimental trials between the months of February and early April. The experimental trials for 2 of the subjects were conducted in late May into early June. Experiments were conducted following a 48 hour period without physical activity and subjects were instructed to avoid excessive perambulation or other stresses during the period between awakening and experimentation such as exposure to hot or cold temperatures and excessive physical activity during transit from home to the laboratory. Further, they were asked to fast at least 4 h prior to experimentation but were permitted water *ad libitum* during this time.

Pre-warming phase

Upon arrival to the laboratory, subjects clothed in shorts and athletic shoes were fitted with the appropriate instruments and donned the liquid conditioned suit. Each of the two experimental trials commenced at approximately 9h00. Subjects were initially habituated at an ambient temperature of 22°C which was maintained for the duration of the experimental trial (Figure 1). The bretylium tosylate was applied during this habituation period. The α-adrenergic blockade was verified after 90 min. Mean skin temperature was first held at ~33.5°C for ~15 min with the aid of the liquid conditioned

suit perfused with 33.5°C water by use of a temperature-controlled circulation bath (Endocal, NESLAB and model200-00, Micropump, Vancouver, WA). The water perfusate was then rapidly changed to 2°C, and skin cooling continued for 3 min. Changes in cutaneous vascular conductance at both forearm skin sites were used to verify the effectiveness of the vasoconstrictor system blockade (33) prior to the continuation of the experimental trial. After verification of blockade, the liquid conditioned suit was removed.

The subjects were then required to either perform 15-min of cycling on a Monark cycle ergometer at ~70% of their pre-determined $\dot{V}O_{2peak}$ (Exercise) (actual calculated work rate was equal to 72.4% of $\dot{V}O_{2peak}$) or remain resting (No-Exercise) for 15 min. 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 15-min resting recovery at an ambient temperature of 22°C.

Warming phase

Subjects then donned the liquid conditioned suit. Mean skin temperature was clamped at ~33.5°C for ~15 min. Mean skin temperature was then increased at a rate of $4.3 \pm 0.8°C \cdot hr^{-1}$ as the water circulating through the suit was progressively increased to 48°C. Whole-body warming continued until the skin blood flow achieved a sustained elevated value. As previously noted, local skin temperature at the probe holder was maintained at 33.5°C throughout the experimental protocol.

At the end of each experiment, local skin temperature at the bretylium-treated and untreated forearm skin sites was raised to 43°C until peak cutaneous vascular conductance was measured (~30 min). Peak cutaneous vascular conductance was determined as a sustained elevated plateau in local skin blood flow (25, 33). Local warming was immediately followed by a second 3-min cold stress to verify the persistence of the α-adrenergic blockade.

Data and statistical analysis

The onset threshold for cutaneous vasodilation was taken to be the esophageal temperature at which there was an increase in cutaneous vascular conductance measured on the ventral surface of the forearm, observed in three consecutive measurements (33). Thermal sensitivity was defined as the slope of the linear portion of the cutaneous vascular conductance-esophageal temperature relationship as measured during whole-body warming postexercise (33). The linear portion of this curve was selected by visual inspection, and the slopes were determined by least squares linear regression analysis. The average response of the different physiological variables was compared for each condition by using ANOVA with repeated measures. In the event of statistical significance ($P < 0.05$), a Tukey test was used to identify significant differences. All values presented as means ± SE.

RESULTS

Application of cold stress induced a significant reduction in cutaneous vascular conductance at the untreated skin site prior to and after the experimental protocol for all trials (mean value for all trials). Respectively, these values were 14.9 ± 1.5% to 11.2 ±

1.0% change of peak cutaneous vascular conductance and 78.7 ± 2.7% to 63.0 ± 3.6% of peak cutaneous vascular conductance. Bretylium tosylate application blocked the cold-induced reduction in cutaneous vascular conductance prior to and after exercise for all trials demonstrating effective and persistent sympathetic vasoconstrictor blockade at these forearm skin sites. The values were 34.0 ± 3.6% to 36.0 ± 3.9% of peak cutaneous vascular conductance and 85.8 ± 2.4 % to 87.5 ± 1.7 % of peak cutaneous vascular conductance respectively.

Pre-warming phase

Resting heart rate, mean arterial pressure, esophageal temperature and mean skin temperature were similar for all conditions during baseline resting (Table 2).

Hemodynamic response

As shown in Table 2, the postexercise pre-warming (i.e., measurement taken at 30-min post-treatment) mean arterial pressure remained significantly reduced relative to the baseline resting reference value following exercise for both males (-9 mmHg) and females (-14 mmHg) ($P < 0.05$). The value of 14 mmHg for females was significantly greater than the 9 mmHg measured in the male counterparts. Mean arterial pressure remained unchanged throughout the no-exercise trial.

End-exercise heart rates were 157 ± 4 beats·min^{-1} and 161 ± 5 beats·min^{-1} for males and females respectively. For all exercise trials, heart rate remained significantly elevated ($P < 0.05$) above baseline rest values for the 15 min postexercise recovery period. Pre-warming heart rate, as measured at 30-min post-treatment, was significantly

elevated above baseline resting by 16 beats·min^{-1} and 19 beats·min^{-1} for males and females respectively ($P < 0.05$).

Thermal response

The mean thresholds for cutaneous vasodilation measured during exercise are presented in table 3. The mean threshold for cutaneous vasodilation was significantly greater in the females as compared to the males for both the untreated and bretylium-treated sites ($P < 0.05$) (Fig. 2).

Exercise resulted in a significant increase in esophageal temperature of 1.00 ± 0.10°C and 1.09 ± 0.11°C above baseline resting for the male and female subjects respectively ($P < 0.05$). Postexercise esophageal temperature remained significantly elevated above baseline resting by 0.28°C in males and 0.35°C in females respectively at 15-min ($P < 0.05$). However, esophageal temperature returned to near baseline resting at 30-min postexercise prior to the start of whole-body warming. Mean skin temperature also returned to baseline resting values during this period (Table 2). Esophageal temperature and mean skin temperature for the no-exercise condition remained unchanged from baseline resting.

Warming Phase

Mean skin temperature was increased at the same rate of ~4.3 ± 0.8°C·hr^{-1} during the whole-body warming maneuver for all subjects in all conditions.

Cutaneous vasodilation

The postexercise threshold for cutaneous vasodilation was significantly elevated above no-exercise resting for males and females respectively (Fig. 3). We observed a large difference in the magnitude of the measured thresholds between males and females

equal to 0.21°C and 0.26°C for the untreated and treated sites respectively (Fig. 3). In contrast, no gender difference in the onset threshold for cutaneous vasodilation was measured for the no-exercise trial. These results, as well as those from no-exercise resting are presented in Table 4. In addition, figure 4 depicts the relative increase in the thresholds relative to baseline resting esophageal temperature.

Postexercise thresholds measured at the untreated forearm site increased by 0.21°C and 0.37°C above no-exercise controls for males and females respectively. Similar increases of 0.19°C and 0.39°C were measured for the bretylium-treated site. Mean skin temperature at the onset threshold for cutaneous vasodilation was similar for all conditions (Table 4). The sensitivity of the thermal reflex was estimated from the slope of the linear relationship between cutaneous vascular conductance and esophageal temperature. The rate of rise of cutaneous vascular conductance per unit change in esophageal temperature was not significantly different between exercise and no-exercise control for either males or females.

DISCUSSION

The postexercise elevation in the threshold for cutaneous vasodilation is in agreement with previous findings (16, 25, 26). However, we observed a difference in the magnitude of the measured thresholds between males and females. The greater threshold in females was accompanied by a more pronounced decrease in the postexercise mean arterial pressure response relative to the males. These observations support our hypothesis that females would demonstrate a greater reduction in mean arterial pressure and concurrently a greater increase in the postexercise core temperature at which onset of

cutaneous vasodilation occurred as compared to males. Furthermore, the similarity of the response of the postexercise resting threshold measured at the untreated and bretylium-treated sites in both males and females, suggests that the primary mechanism for the difference likely results from modulation of active vasodilatory activity and not from increased adrenergic vasoconstrictor tone.

Threshold for Vasodilation during Exercise

An increase in the exercise threshold for cutaneous vasodilation was measured in both males and females and was similar for both the untreated and bretylium-treated sites which is consistent with previous findings. However, we showed that the magnitude of the exercise increase in the threshold for cutaneous vasodilation was greater in females as compared to males. This observation is consistent with the findings of Roberts et al. (38) who reported a higher threshold for skin blood flow in females as compared to males as measured during exercise. Thus, the difference in the magnitude of the threshold associated with an increase in exercise skin blood flow may be the result of differences in males and females thermal sensitivity (7). In contrast, Kolka et al. (28) reported no gender differences in the threshold or thermal sensitivity during exercise performed in hot ambient conditions. Differences in the pattern of thermoregulatory control in skin and active muscle blood flow associated with the combined stress of exercise and hot ambient temperature may in part explain the discrepancy in the observed responses reported in these studies (1).

Postexercise Thermal Response

The observation of a postexercise elevation in core temperature measured in both males and females subjects as recorded at 15-min postexercise is noteworthy. This

observation is consistent with the previous reports of a sustained elevation in core temperature postexercise in male subjects (16, 22, 43).

The observed postexercise increase in the threshold for cutaneous vasodilation measured following a short recovery are similar to previous findings (16, 23, 25, 26). These previous studies however present a possible inherent bias in that they were either conducted on male subjects exclusively or did not include enough females to determine possible gender differences. Although we report a postexercise increase in the onset threshold for males and females, we observed that this postexercise elevation in the warm response threshold of cutaneous vasodilation is significantly greater in females as compared to males.

Consistent with previous observations (23), we observed an increase in the postexercise threshold when passive whole-body warming was initiated during the period of postexercise hypotension. Further, a greater increase in the postexercise threshold for females was paralleled by a greater reduction in mean arterial pressure. Although it is possible that this relationship is merely fortuitous, recent evidence would suggest otherwise. For example, it has previously been shown that an increase in the postexercise hypotensive response, induced by exercise of increasing intensity, was shown to result in a relative increase in the onset threshold for cutaneous vasodilation in males (26). Studies have shown that different recovery modes (i.e., inactive, passive or active recovery mode) impact the role of nonthermal (i.e, central command, baroreceptors, and muscle mechanoreceptors) influences on postexercise skin blood flow (3, 18, 46). Specifically, these studies show that skin blood flow during inactive recovery is influenced primarily by baroreceptors. Furthermore, restoration of mean arterial pressure through application

of positive pressure to the lower limbs was shown to reverse the postexercise increase in the threshold for cutaneous vasodilation (16) and also increase whole body heat loss (17).

The postexercise hemodynamic response, as represented by heart rate and mean arterial pressure, is consistent with postexercise hypotension (5, 24, 31). There have been many reports of reduced tolerance in the face of an orthostatic challenge in females compared to males (6, 12, 13, 40, 44). This response is subsequent to a reduced mean arterial pressure and reduced compensatory vasoconstriction in females than in males (2). Implicit in the evidence that females have reduced tolerance to orthostatic challenge is the observation that females regulate blood pressure via different mechanisms (2, 39). Moreover studies show that females have less effective baroreflex buffering of arterial blood pressure as compared to their males counterparts (4). It has also been shown that females appear to have an attenuated responsiveness in the mechanisms that regulate arterial pressure (6, 13). It is plausible therefore, that given the orthostatic effect of the upright seated posture during exercise recovery employed in our study in combination with the decreased responsiveness of cardiovascular mechanisms to regulate arterial pressure in females may have resulted in the greater postexercise hypotension. In parallel, it has been shown that acute reductions in central venous pressure delay or decrease the rise in skin blood flow (33, 34) which may explain our observation of a gender difference in the onset threshold for cutaneous vasodilation.

It should be noted that while the study by Senitko et al. (39) did not show a postexercise hypotension in their endurance trained individuals, they reported a gender difference in postexercise hypotension in their sedentary group in the upright posture. While our subjects were considered fit they did not meet the criteria of 20-60 miles per

week as outlined in their study. Of note, the maximal oxygen consumption values of the participants in the study by Senitko et al. (39) were not reported and thus we cannot make a comparison with our subjects. However, we estimate the fitness level of our subjects to between that of the sedentary and endurance trained participants which may explain our observed gender difference in the postexercise hypotension response.

Limitations of this investigation

Factors such as aerobic fitness, heat acclimation, hydration status and sex hormones may explain the gender differences in exercise and postexercise skin blood flow response between males and females (10, 38). Further, these differences between males and females may be attributed to: 1) a larger ratio of body surface to body mass; 2) a greater subcutaneous fat content; and, 3) a lower exercise capacity. However, it has been shown that these differences are reduced when male and female groups are matched for physical fitness (19, 29, 30, 41, 42, 47). In our study the male and female subjects were matched for age and physical fitness (based on $\dot{V}O_2$peak expressed per kg of fat-free mass). Furthermore, neither group was likely heat acclimated as the 12 of the 14 subjects completed their experimental trials between the months of February and early April. The female subjects were studied during the early follicular phase of their menstrual cycle to reduce the influence of hormone-mediated modulation of exercise skin blood flow response.

It is possible that differences in hydration status may explain our observations of gender difference in the postexercise onset threshold for cutaneous vasodilation. Studies have shown that hypohydration increases the threshold for cutaneous vasodilation (10) and that the magnitude of the response is dependent on the level of hypohydration.

However, it has been shown that sweating rates are generally lower in women than in men (11). Further, as noted by Senitko et al. (39), it is likely that the male subjects had a greater sweating-related fluid loss, subsequently losing more plasma volume and undergoing greater reductions in central venous pressure. Thus, we would have expected a greater increase in the onset threshold for males as compared to females. Furthermore, the hydration status of our subjects was not verified during the experiment because it was unlikely that any significant hypohydration occurred given the type and duration of the exercise. Montain and Coyle (36) demonstrated that 2 h of dynamic exercise at 65% of $\dot{V}O_2$max performed in a warm environment (33°C) with no water intake results in a maximum weight loss of 4.2%. Similarly, Mack and Nadel (32), noted that a 70-kg adult could potentially lose on the order of 2.5% of water content per hour of heavy exercise in the heat owing primarily to water loss from sweating. In our study, the short duration of moderate intensity exercise performed in a cooler environment with unrestricted pretrial water intake is unlikely to have caused more than a 0.5% weight loss. Under this condition, our subjects could be considered euhydrated (14).

In summary, our findings support the hypothesis that there is a possible physiological link between the observed postexercise cardiovascular changes and the altered thermal response thresholds for cutaneous vasodilation which is influenced by gender. The greater onset threshold measured in females as compared to males could be due to 1) an alteration of vasodilator outflow due to baroreceptor unloading or 2) a baroreceptor-mediated increase in adrenergic vasoconstrictor tone. Our demonstration of a similar threshold for cutaneous vasodilation at the untreated and bretylium-treated forearm sites would suggest that the primary mechanism of control for the gender

difference in postexercise skin blood flow is likely the result of an altered active vasodilatory response and not an increase in adrenergic vasoconstrictor tone.

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TABLES

Table 1. *The physical characteristics of the subjects.*

	Males	**Females**
Age (yr)	24 ± 1	24 ± 0.9
Height (cm)	176.9 ± 2.0	165.4 ± 1.8 *
Weight (kg)	82.1 ± 1.7	62.4 ± 2.7 *
BSA/mass	0.0242 ± 0.001	0.0269 ± 0.001
Body fat (%)	18.4 ± 0.9	20.7 ± 1.2
Maximal oxygen consumption, $VO_{2\ peak}$ (ml/min*kg)	52.0 ± 1.7	47.9 ± 2.4
Maximal oxygen consumption, $VO_{2\ peak}$ (ml/min*kgFFM)	63.6 ± 1.9	60.5 ± 2.6

Values are means ± SE; BSA, body surface area; FFM, fat-free mass; *, indicates significant difference from males subjects ($P < 0.05$).

Table 2. *Hemodynamic and core and skin temperatures during baseline resting and prewarming for all conditions.*

	No Exercise		Exercise	
	Males	Females	Males	Females
MAP, mmHg				
Baseline resting	93 ± 5	92 ± 3	93 ± 3	93 ± 4
15 min post-treatment	93 ± 4	93 ± 3	86 ± 3†	80 ± 3*†
30 min post-treatment	91 ± 5	92 ± 4	84 ± 3†	79 ± 3*†
HR, beats·min^{-1}				
Baseline resting	59 ± 4	65 ± 4	61 ± 3	68 ± 4
15 min post-treatment	61 ± 4	63 ± 3	79 ± 4†	88 ± 5*†
30 min post-treatment	60 ± 5	61 ± 4	77 ± 4†	87 ± 6*†
T_{es}, (°C)				
Baseline resting	36.88 ± 0.06	36.86 ± 0.07	36.91 ± 0.04	36.95 ± 0.05
15 min post-treatment	36.87 ± 0.05	36.96 ± 0.05	37.19 ± 0.05†	37.30 ± 0.06†
30 min post-treatment	36.90 ± 0.05	36.98 ± 0.06	36.97 ± 0.07	37.05 ± 0.07
$\bar{T}_{sk}$, (°C)				
Baseline resting	33.39 ± 0.13	33.41 ± 0.19	33.32 ± 0.21	33.43 ± 0.14
15 min post-treatment	33.01 ± 0.16	32.99 ± 0.14	33.61 ± 0.18	33.72 ± 0.18
30 min post-treatment	33.37 ± 0.21	33.41 ± 0.23	33.56 ± 0.25	33.61 ± 0.26

Values are means ± SE. Note: post-treatment period represents the time period following either 15 min exercise at 70% of $\dot{V}O_{2peak}$ (Exercise) or 15 min of seated rest (No-Exercise). MAP, mean arterial pressure; HR, heart rate; T_{es}, esophageal temperature; $\bar{T}_{sk}$, mean skin temperature. *, indicates significant gender difference, $P < 0.05$; †, indicates significant increase from no-exercise, $P < 0.05$.

Table 3. *Esophageal and mean skin temperature at the onset threshold for forearm cutaneous vasodilation during exercise at the bretylium treated and untreated sites*

	Males	Females
T_{es} (°C)		
Untreated	37.33 ± 0.06 *	37.51 ± 0.08
Bretylium Treated	37.35 ± 0.06 *	37.58 ± 0.04
$\bar{T}_{sk}$, (°C)		
Untreated	32.36 ± 0.23	32.29 ± 0.20
Bretylium Treated	32.51 ± 0.22	32.30 ± 0.19

Values presented are means ± SE. T_{es}, esophageal temperature; $\bar{T}_{sk}$, mean skin temperature. * , indicates significant gender differences ($P < 0.05$).

Table 4. *Esophageal and mean skin temperature at the onset threshold for forearm cutaneous vasodilation for no-exercise and postexercise resting at the bretylium treated and untreated sites for all conditions.*

	No-exercise		Exercise	
	Males	Females	Males	Females
T_{es} (°C)				
Untreated	36.94 ± 0.07	36.99 ± 0.09	37.15 ± 0.03*†	37.36 ± 0.05 †
Bretylium Treated	36.97 ± 0.05	37.03 ± 0.11	37.16 ± 0.04*†	37.42 ± 0.07 †
$\bar{T}_{sk}$, (°C)				
Untreated	36.14 ± 0.10	36.24 ± 0.09	36.33 ± 0.11	36.50 ± 0.10
Bretylium treated	36.20 ± 0.10	36.26 ± 0.11	36.46 ± 0.08	36.48 ± 0.09

Values presented are means ± SE; T_{es}, esophageal temperature; $\bar{T}_{sk}$, mean skin temperature. * , indicates significant gender difference, $P < 0.05$; †, indicates significant increase from no-exercise, $P < 0.05$.

FIGURES

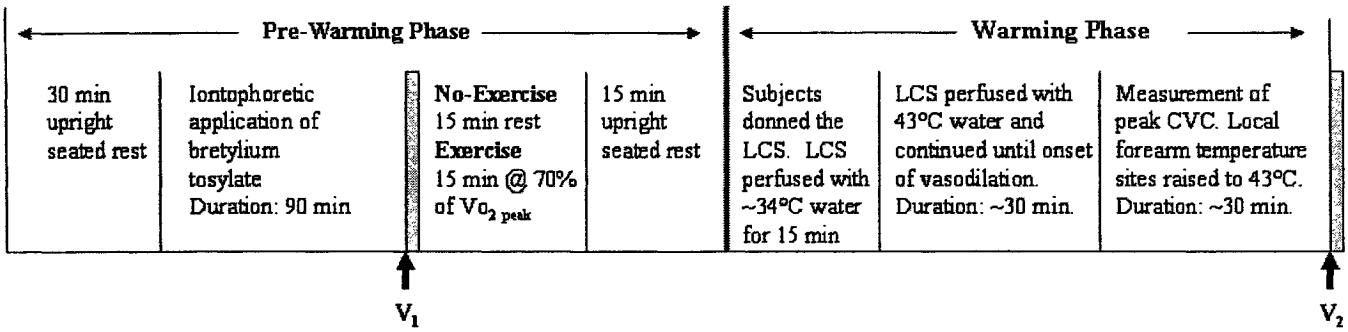

Figure 1. Experimental protocol time line. $VO_{2\ peak}$, peak oxygen consumption; LCS, liquid conditioned suit; CVC, cutaneous vascular conductance; and, V, verification of α-adrenergic blockade during pre-warming (V_1) and post-warming phases (V_2).

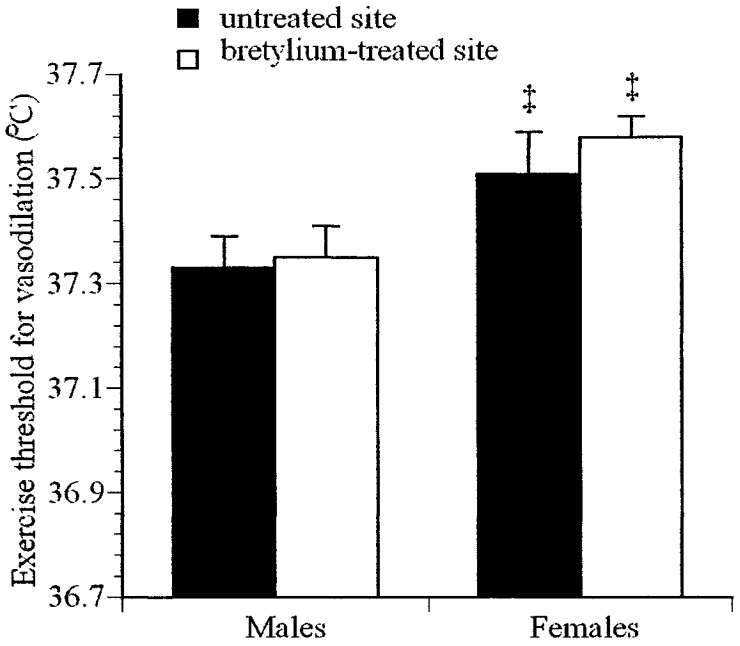

Figure 2. Mean (±SE) onset esophageal temperature threshold values for forearm cutaneous vasodilation measured during moderate (70% of $\dot{V}O_{2peak}$) intensity exercise for males and females. Filled bars, untreated forearm measurement site; open bars, bretylium-treated measurement site. ‡, indicates significant gender difference ($P < 0.05$).

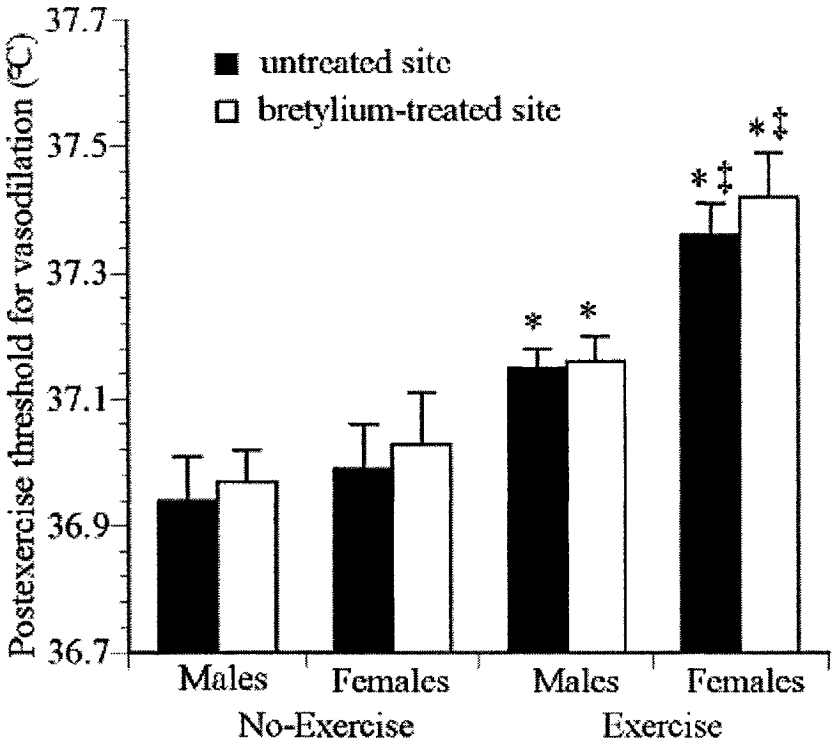

Figure 3. Mean (±SE) onset esophageal temperature threshold values for forearm cutaneous vasodilation for no-exercise and postexercise resting for the bretylium-treated and untreated forearm measurement sites in males and females. Filled bars, untreated forearm measurement site; open bars, bretylium-treated measurement site. Exercise resulted in significant increase in the threshold for cutaneous vasodilation above no-exercise resting (*, $P < 0.05$). ‡, indicates significant gender difference ($P < 0.05$).

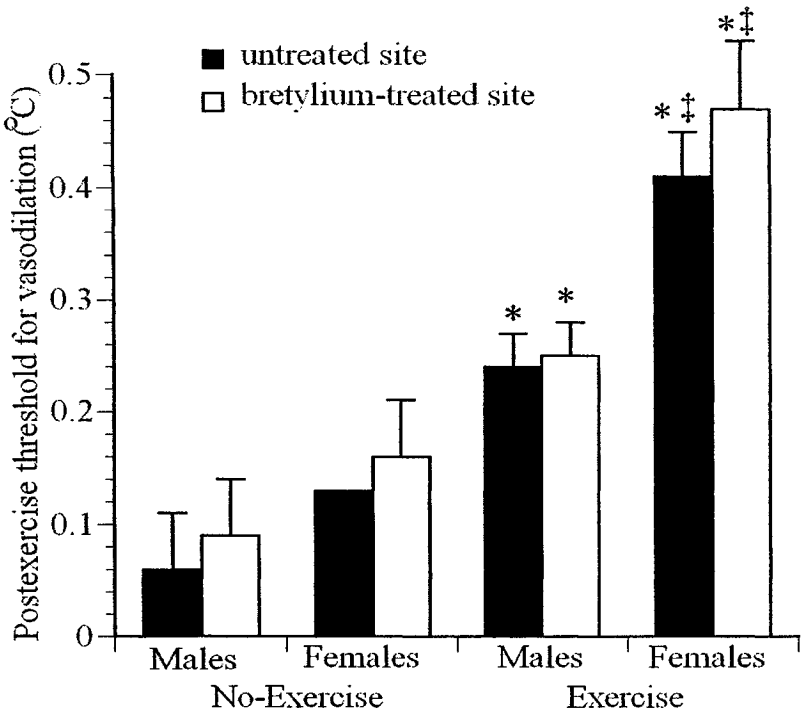

Figure 4. Mean (±SE) relative onset esophageal temperature threshold values for forearm cutaneous vasodilation for no-exercise and postexercise resting for the bretylium-treated and untreated forearm measurement sites in males and females. Values represent relative increases from baseline resting esophageal temperature values. Filled bars, untreated forearm measurement site; open bars, bretylium-treated measurement site. Exercise resulted in significant increase in the threshold for cutaneous vasodilation above no-exercise resting (*, $P < 0.05$). ‡, indicates significant gender difference ($P < 0.05$).

CHAPTER V

CONCLUSION

The purpose of this study was to examine the differences between males and females in the postexercise threshold for cutaneous vasodilation, as well as evaluate the mechanism of skin blood flow control during this postexercise period.

Exercise induces a residual effect on thermal control resulting in an increase in the postexercise core temperature at which cutaneous vasodilation occurs (Jackson and Kenny, 2003; Kenny et al., 2000, Kenny et al., 2000b). Moreover, this postexercise increase in the threshold for vasodilation is consistent with a baroreceptor-mediated attenuation of skin blood flow, subsequent to lower body venous pooling and decreases in mean arterial pressure (Jackson and Kenny, 2003). In the present study women had significantly greater decreases in mean arterial pressure following exercise compared with men. Consistent with this observation was the finding that women also had a greater increase in the postexercise esophageal temperature threshold for cutaneous vasodilation in comparison to men. On the basis of previous observations, it is plausible that our findings of a greater increase in the postexercise threshold for cutaneous vasodilation in women compared to men is attributable to a baroreceptor-mediated attenuation of postexercise skin blood flow, subsequent to greater decreases in mean arterial pressure. Furthermore, we showed a similar threshold for vasodilation at the bretylium treated and untreated forearm sites in both men and women. This suggests that the primary mechanism of control for the increase in the postexercise threshold for vasodilation is the

result of a delay in the active vasodilatory response as opposed to an increase in vasoconstrictor activity.

The present study also gave insight into differences between men and women during exercise. The core temperature threshold for cutaneous vasodilation was elevated above no-exercise resting in all subjects, with women displaying a higher core temperature at the onset of cutaneous vasodilation compared with men. The greater attenuation in skin blood flow during exercise observed in women may be related to a more prolonged initial vasoconstriction accompanying the onset of exercise to ensure adequate blood flow to the exercising muscle and to maintain blood pressure. Similar to our postexercise findings, we showed that the threshold for vasodilation during exercise at the bretylium treated and untreated forearm sites in both men and women were not different, suggesting that the attenuation in skin blood flow is the result of a delay in the active vasodilatory response as opposed to an increase in vasoconstrictor activity.

In conclusion, women may be at increased risk for postexercise hypotension as well as experience a greater delay in the postexercise onset esophageal temperature threshold for cutaneous vasodilation when compared with men. Skin blood flow facilitates heat loss and therefore altered control of skin blood flow in females during exercise recovery may result in a decreased ability to dissipate heat.

CHAPTER VI

APPENDICES

HEALTH SCIENCES AND SCIENCES RESEARCH ETHICS BOARD

CERTIFICATE OF ETHICAL APPROVAL

This is to certify that the University of Ottawa Health Sciences and Sciences Research Ethics Board has examined the application for ethical approval for the research project **Gender Differences in the Resting Post-Exercise Threshold for Cutaneous Vasodilation (file: H 11-03-02)** submitted by Jane Murrin, who is supervised by Glen Kenny, both of the School of Nursing, Faculty of Health Sciences. The Board found that this research project met appropriate ethical standards as outlined in the Tri-Council Policy Statement and in the Procedures of the University of Ottawa Research Ethics Boards, and accordingly gave it a Category 1a (approval). This certification is valid for one year from the date indicated below.

January 7, 2004

Rita D'Alessandro
Protocol Officer for Ethics in Research,
For the Chairperson of the Health
Sciences and Sciences REB
Daniel Lagarec

the study you will complete an informed consent form, a health questionnaire and the Physical Activity Readiness Questionnaire (Par-Q) to determine if there are any reasons why you should not participate in this study or perform exercise. If you meet the criteria you will be asked to participate in a short screening process where we will first assess your body composition by means of hydrostatic weighing, where you will be required to submerge your head and hold your breath under water for approximately 3-5 seconds. We will then evaluate your suitability for future testing by inserting the esophageal probe to ensure that you are comfortable with the procedure and the use of the probe. Once inserted you will be asked to remain seated for no less than 10 min to ensure no ill effects or discomfort from the probe insertion. An incremental maximal oxygen consumption test (VO_2 max test) will then be performed, which is a measure of aerobic fitness. During the VO_2 max test you are encouraged to exercise to exhaustion. You will be asked to cycle at 60rpm and workload will be increased to 1.5kp and then increased by 0.5kp every 2 minutes until you reach your maximal voluntary limit, as indicated by you. The pertinent data will be collected using a Polar heart rate monitor and metabolic cart, which will require you to wear a nose plug and a mouth piece that you will breathe into. This data will be used to select the workload at which you are to cycle for the submaximal exercise during the experimental trials. The risks and discomforts of the maximal exercise testing are nausea and dizziness. The incidence of cardiac arrest during maximal exercise tests is 1 in 10,000 tests. The "Guidelines for Graded Exercise Testing and Exercise Prescription" (by the American College of Sports Medicine) indicate that maximum exercise testing for men under 40 years of age and women under 50 years of age, with no symptoms of risk factors for cardiovascular disease, do not require the presence a physician during the tests. At any time during this test you may stop.

The remaining trials will be conducted in the morning following a 24-hour period without physical activity. On each of the study days you must refrain from stimulants and alcohol for 12 hours prior to each trial. Subjects will refrain from eating and drinking anything other that a minimum of 0.25 liters of water during each waking hour and encouraged to ingest water ad libitum during the preparatory period. On the day of testing, care will be taken to avoid thermal stimuli or any major increase in metabolic rate between awakening and the start of the experiment. All trials will be conducted during the winter months.

During each experimental session it will be required that you are clothed in shorts or a sports bra and shorts for women. It will be necessary to equip you with instruments to measure heart rate, blood flow, blood pressure, cardiac output, skin temperature, internal temperature, sweat rate and oxygen consumption. Finally you will be fitted with a liquid conditioned suit and bretylium tosylate will be applied to your left forearm. Below is a description of the equipment, followed by an explanation of what is required during each experimental trial.

Heart rate - The Polar Heart Rate monitor, which includes a chest strap and watch, will be used to monitor heart rate.

Skin Blood Flow – Skin blood flow will be measured using a Perimed flexible laser probe on the surface of the skin at the mid-forearm. This device does not cause any discomfort or residual effects.

Blood pressure – Blood pressure will be measured using a Finapress (model 2300) blood pressure monitor. This monitor measures arterial blood pressure using a non-invasive technique and a finger cuff for measuring blood flow by plethysmography (blood pressure cuff is inflated and a pulse volume recorder measures each pulse wave). Blood pressure will also be measured manually at pre-determined intervals using sphygmomanometer and a stethoscope. Mild pressure may be experienced during the readings at the arm and the finger.

Cardiac Output – The indirect Fick Method with carbon dioxide rebreathing will be used to measure cardiac output. This is a non-invasive standard technique suitable for human subjects where you will be required to rebreath an initial gas mixture of 4% carbon dioxide. You will wear a mouthpiece, which will be connected to the cardiac output analyzer, and a nose plug. The carbon dioxide in the gas mixture is not much more than normal carbon dioxide content in the air; however, it is possible that you may experience slight dizziness during exercise. The test lasts for only 20 seconds and this sensation passes as soon as the test is complete.

Skin thermistors – 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 with a disposable razor in order to secure the probes adequately to the skin surface. Some discomfort may be experienced upon removing the tape.

Esophageal probe – In order to monitor central body temperature, a flexible esophageal temperature probe (2mm in diameter) will be inserted through one nostril, while you swallow sips of water. The tip of the probe, once fully inserted in the esophagus (swallowing tube), will rest at the level of the heart. There can be mild discomfort and a mild gagging reflex from swallowing the probe that will pass. You should be aware that there is some risk associated with the insertion of the esophageal probe. The insertion of the esophageal probe may cause some minor irritation and mild gagging reflex during insertion especially if it is the first time receiving an esophageal probe. However, lubricant is available upon request for the probe and the mild irritation and gagging reflex soon passes. Perforation of the esophagus or oral or nasal cavities could occur during insertion of the esophageal probe (potentially causing inflammation and infection). However, such an incident is rare and no such incident has ever occurred in this laboratory. The risk of transmission of infectious disease is negligible as each participant has his own sterile probe that will be disposed of once all tests have been completed.

Sweat capsule – sweat rate will be estimated from a 5.0 cm^2 capsule placed on your upper back and ventilated with anhydrous compressed air (air containing no water that is under pressure greater than that of the atmosphere). This device does not cause any

discomfort or residual effects. The capsule will be taped to the upper back and therefore, you may experience some discomfort when removing the tape.

Metabolic Cart – An automated metabolic cart (Moxus) will be used to assess oxygen consumption, carbon dioxide production and ventilation. You will be required to wear a plastic mouthpiece that is connected to the metabolic cart and a nose plug.

Liquid conditioned suit – Cold (2°C) and hot (48°C) water will be circulated through the liquid conditioned suit throughout the experiment during both sessions. The liquid conditioned suit fits tightly to the body and contains water-perfused tubes. The temperature of the water flowing through the tubes can continually be adjusted using the temperature controlled circulation bath to adjust heat loss and heat gain. The use of this suit may cause slight discomfort as it is being used to decrease and elevate skin temperature.

Bretylium Tosylate - Bretylium tosylate is a drug that selectively blocks the constriction of vessels in its area of application, without modifying vasodilation. Therefore, the vessels in this area will not be able to constrict but will be able to dilate. Bretylium tosylate is applied by iontophoresis with a Perilont micropharmacology system PF480-1 (Perimed) to 1.0 cm^2 of skin on the ventral side of the left forearm. The Perilont system uses a disposable drug delivery electrode (PF 481-1) in which a 10 mM solution of bretylium tosylate in propylene glycol is absorbed. Iontophoresis is an effective and painless method of delivering medication to a localized tissue area by applying electrical current to a solution of the medication. Like electrical charges repel and therefore, application of a positive current will drive positively charged drug molecules away from the electrode and into the tissues; similarly, a negative current will drive negatively charge ions into the tissues. The application of bretylium tosylate has been performed in our laboratory in the past and causes no discomfort or residual effects.

For each session, you will be required to participate in a pretreatment period, a treatment period and a post-treatment period.

Pretreatment period. Upon arrival, you will be weighed wearing only shorts, running shoes, and a sports bra for women, and then instrumented appropriately with the thermal probes, esophageal probe, laser-Doppler blood flow sensor (mid-forearm), Finapress 2300 finger blood pressure cuff (middle finger), sweat capsule, cardiac output mouthpiece and heart rate monitor. You will also be fitted with the liquid conditioned suit and spandex pants. The bretylium tosylate will be applied to the ventral side of your left forearm and you will be placed in an upright semi-seated position at an ambient temperature of approximately 22°C. The α-adrenergic blockade will be verified after 90 minutes. Your mean skin temperature will first be held at ~33.5°C for 15 minutes with the aid of the liquid conditioned suit being perfused with 33.5°C water. The water perfusate will then be rapidly changed to 2°C and skin cooling continued for 3 minutes. Changes in cutaneous vascular conductance (skin blood flow divided by mean arterial pressure) at both forearm skin sites will be used to verify the effectiveness of α-

For each testing session, I will be required to participate in a pretreatment period, a treatment period and a post-treatment period.

Pretreatment period. Upon arrival, I will be weighed wearing only shorts, running shoes, as well as a sports bra for women, and then instrumented appropriately with the thermal probes, esophageal probe, laser-Doppler blood flow sensor (mid-forearm), Finapress 2300 finger blood pressure cuff (middle finger), sweat capsule, cardiac output mouthpiece and heart rate monitor. I will also be fitted with the liquid conditioned suit and spandex pants. Bretylium tosylate will be applied by iontophoresis to the ventral side of my left forearm and I will be placed in an upright semi-seated position at an ambient temperature of approximately 22°C. The α-adrenergic blockade will be verified after 90 minutes. My mean skin temperature will first be held at ~33.5°C for 15 minutes with the aid of the liquid conditioned suit being perfused with 33.5°C water. The water perfusate will then be rapidly changed to 2°C and skin cooling continued for 3 minutes. Changes in cutaneous vascular conductance (skin blood flow divided by mean arterial pressure) at both forearm skin sites will be used to verify the effectiveness of α-adrenergic blockade before the continuation of the experimental trial. After verification of blockade the liquid conditioned suit will be removed.

Treatment period. Immediately following the pretreatment period I will either be asked to exercise or remain at rest. For the exercise treatment, I will perform 15 minutes of cycle ergometer exercise at 70% of my maximal oxygen uptake. For the no exercise treatment, I will rest in the semi-seated upright position for 15 minutes. I will then either be moved to (exercise) or remain in (no exercise) the semi-seated upright position to complete 15 minutes of resting recovery at an ambient temperature of ~22°C.

Posttreatment period. Immediately following the exercise and no exercise treatment period, I will be placed back into the liquid conditioned suit. Mean skin temperature will be clamped at ~33.5°C for ~15 minutes by using the liquid conditioned suit perfused with 33.5°C water. My mean skin temperature will then be increased as the water circulating through the suit is progressively increased to 48°C. Whole body warming will continue until skin blood flow achieves a sustained elevated value.

At the end of each experiment, local skin temperature at the bretylium-treated and untreated forearm skin sites will be raised to 43°C until peak (sustained elevated plateau) cutaneous vascular conductance is measured (~30 minutes). Warming will be immediately followed by a second 3-minute cold stress to verify the persistence of the α-adrenergic blockade.

I understand that I am free to withdraw from the experiment at any time without prejudice or discrimination of any form.

I am aware and accept that there is some risk associated with the insertion of the esophageal probe. The insertion of the esophageal probe may cause some minor irritation and mild gagging reflex during insertion especially if it is the first time receiving an esophageal probe. However, lubricant is available upon request for the probe and the mild irritation and gagging reflex soon passes. Perforation of the esophagus or oral or nasal cavities could occur during insertion of the esophageal probe (potentially causing inflammation and infection). However, such an incident is rare and no such incident has ever occurred in this laboratory. The risk of transmission of infectious disease is

APPENDIX B-3: QUESTIONNAIRE

Questionnaire for the possible participation to the study entitled "Gender Differences in the Resting Post-exercise Threshold for Cutaneous Vasodilation"

Could you please fill out the following questions:

1. Are you aged between 19 to 30 years old? Yes☐ No☐

2. Have you seen a physician in the past year for a full physical exam? Yes☐ No☐

3. Do you or did you ever suffer from medical or health problems? Yes☐ No☐
   If yes, please specify:
   _____
   _____
   _____

4. Are you on any medications? Yes☐ No☐
   If yes, please specify:
   _____
   _____
   _____

5. Do you smoke? Yes☐ No☐

6. Females please fill out the following 4 questions:

   A) Are you currently pregnant? Yes☐ No☐

   B) Are you planning to conceive in the near future? Yes☐ No☐

   C) Are you on the birth control pill? Yes☐ No☐

   E) Are you doing anything to compromise the regularity of your menstrual cycle, such as excessive training, undereating, under excessive stress? Yes☐ No☐

7. Please fill out the PAR-Q and you questionnaire (Physical Activity Readiness Questionnaire) at the end of this package.

8. Based on the last 2-3 months, please answer the following questions:

   A) Over a typical seven-day period (one week), how many times do you engage in physical activity that is sufficiently prolonged (at least 20 minutes) and intense to cause sweating and a rapid heart beat?

   At least three times ☐

Normally once or twice ☐

Rarely or never ☐

B) When you engage in physical activity, do you generally have the impression that you:

Make an intense effort ☐

Make a moderate effort ☐

Make a light effort ☐

C) In a general fashion, would you say that your current physical fitness condition is:

Very good ☐

Good ☐

Average ☐

Poor ☐

D) Make a list of the activities that you regularly engage in. Indicate the typical length, the frequency (# of times per week), the intensity (light, moderate, hard) and general environmental conditions (indoor/outdoor, cold, hot, warm, humid, dry, etc…) for these activities:

Activity (sport)	**Length**	**Frequency**	**Intensity**	**Conditions**

9. Has your body composition (large weight gain or loss) changed drastically over the past 6 months? Yes☐ No☐
If yes, please specify:

_____

_____

_____

APPENDIX B-4: PHYSICAL ACTIVITY READINESS QUESTIONNAIRE

PAR – Q & YOU

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

(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? 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 with 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-O 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 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.

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.

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

NAME: _____

SIGNATURE: _____ **DATE:** _____
SIGNATURE OF PARENT: _____ **WITNESS:** _____
or GUARDIAN (for participants under the age of majority)

You are encouraged to copy the PAR-Q but only if you use the entire form

APPENDIX B-5: HYDROSTATIC WEIGHING PROCEDURE

Hydrostatic Weighing

Name: Contact info:
Weight: Temperature:
Height: Humidity:
Age: Pressure:

Water temperature:
Water density (Dw):
Gastro intestinal volume: 0.11
Residual Volume (L)

Men: RV = (0.019 x height) + (0.0115 x age) – 2.24

Women: RV = (0.032 x height) + (0.009 x age) – 3.90

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

Body Density (g/ml):

D_b = BM(g) / (BMa(g) – BMw(g) / Dw) – (RV(ml) + 100ml)

Body Fat (%):

Siri = (495 / Db) – 450

Body Density (g/ml)	**Body Fat (%)**

Average Body Fat: %

Comments:

APPENDIX B-6: MAXIMAL OXYGEN UPTAKE PROCEDURE

VO_2max - Cycle

Name: Contact info:
Weight: Temperature:
Height: Humidity:
Age: Pressure:

Estimated VO_2max <3.0 l/min				Estimated VO_2max >3.0 l/min			
Time	**Speed**	**Resistance**	**Heart Rate**	**Time**	**Speed**	**Resistance**	**Heart Rate**
Warm-up				Warm-up			
0-5				0-5			
Rest	**Rest**	**Rest**	**Rest**	**Rest**	**Rest**	**Rest**	**Rest**
Test				Test			
0-2				0-2			
2-4				2-4			
4-6				4-6			
6-8				6-8			
8-10				8-10			
10-12				10-12			
12-14				12-14			
Recovery				Recovery			
0-3				0-3			

VO_2max: ml/kg-min
VO_2max: l/min

Comments: