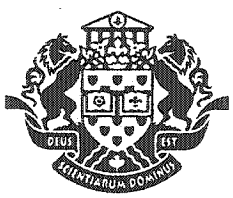

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THERMOREGULATORY AND NONTHERMOREGULATORY INTERACTION IN HUMAN CARDIOVASCULAR CONTROL

WILLIAM SHANE JOURNEAY
B.Sc., University of Ottawa, 2001

THESIS

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I find myself sitting here on my 24th Birthday and on the eve of depositing my thesis wondering where my time at the University of Ottawa has gone. I quickly realize that the time has been very well spent from my perspective and at the same time I have spent the time of many others who have surrounded me during my time here in Ottawa.

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THERMOREGULATORY AND NONTHERMOREGULATORY INTERACTION IN HUMAN CARDIOVASCULAR CONTROL. William Shane Journeay

Purpose: Study #1 examined the responses to facial immersion under states of altered cardiac filling. Study #2 sought to examine changes in postexercise hemodynamics and skin blood flow (SkBF) when lower blood pooling was manipulated using lower body pressure. **Methods:** *Study #1*- Six male subjects participated. They performed 30-s apneic facial immersions under: LBNP, LBPP, during post-exercise hypotension (PEH); & Control. MAP ,HR, and SkBF were measured. *Study #2* - Subjects were exposed to LBNP, LBPP; or no pressure after 15-mins of cycle exercise at 70% of $VO_{2\ peak}$. HR, CO, SV, MAP, TPR, & SkBF, skin and esophageal temperature were recorded. **Conclusions**: *Study #1* - Cardiac parasympathetic response during facial immersion can be attenuated when cardiac filling is compromised. *Study #2* – 1) LBPP accelerates recovery of baseline hemodynamics while LBNP exacerbates the postexercise hemodynamic state relative to control. 2) altering postexercise hemodynamics via LBPP may affect thermal responses.

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ABBREVIATIONS

BPM	Beats per minute
CNS	Central nervous system
CO	Cardiac output
CO_2	Carbon dioxide
ECG	Electrocardiogram
HR	Heart rate
L	Liters
LBNP	Lower body negative pressure
LBPP	Lower body positive pressure
MAP	Mean arterial pressure
Min	Minute
mmHg	Millimeters of mercury
mL	Milliliters
N_2	Nitrogen
O_2	Oxygen
PU	Perfusion units
SkBF	Skin blood flow
SV	Stroke volume
T_{Sk}	Skin temperature
T_{es}	Esophageal temperature
TPR	Total peripheral resistance
$VO_{2\ max\ or\ peak}$	Maximal oxygen consumption

PART ONE:

EMPIRICAL, THEORETICAL AND METHODOLOGICAL CONSIDERATIONS

CHAPTER 1
INTRODUCTION

1.0 Introduction

In thermoregulatory physiology it is well accepted that heat transfer and heat loss occur via mechanisms such as conduction, convection, radiation and evaporation. Such processes are modified by adjustments in regional blood flow and by changes in the external environment. Thus, one's ability to efficiently thermoregulate is limited by the capacity of the cardiovascular system to transport heat to the body's surface via the blood, or to move blood centrally to conserve heat in the face of a cold stimulus. This means that thermoregulatory processes, particularly during heat stress come at a "cost" to the cardiovascular system. If the added strain on the cardiovascular system is not met, either the heat loss response will be attenuated or mean arterial pressure (MAP) will not be maintained and cardiovascular collapse will ensue.

The cardiovascular system has a number of mechanisms in place to maintain mean arterial pressure, many of which are coordinated by the autonomic nervous system. These mechanisms, along with conflicting inputs from thermoregulatory and higher brain inputs ultimately determine whether MAP will be sustained at adequate levels. The maintenance of MAP is of particular interest when conflicting stimuli alter total peripheral resistance and/or cardiac output. Such conflicts occur during recovery from dynamic exercise and during reflex responses such as the human diving response.

This work will be comprised of experiments examining mechanisms of cardiovascular control when faced with various stimuli that alter the status of the cardiovascular system. The first experiment will examine the role of cardiac filling in the development of the human diving response elicited by facial immersion in cold water. Subsequent experiments will examine resting seated

hemodynamics during recovery pressure from exercise and on skin blood flow by modifying lower extremity blood pooling by means of lower body positive and negative pressure. Below is an overview of each of the study areas.

A) ***Cardiovascular responses to apneic facial immersion during altered cardiac filling***

The human diving response is a reflex response whereby apnea and immersion of the face in cold water results in bradycardia and peripheral vasoconstriction (Andersson et al., 2002, 2000, 1998). While it has been suggested that adequate cardiac filling is a requirement for the development of the diving response, it has yet to be demonstrated directly. It is unclear at this time how the response is changed during altered venous return and thus cardiac filling. Only a few studies have implicated reduced venous return in the attenuation of the response. Arnold and Nadel (1993) demonstrated that diving bradycardia can be attenuated subsequent to an increased thermal load induced by exogenous heating in 68°C ambient heat. They contended that the attenuation of diving bradycardia occurs as a result of reduced cardiac filling due to peripheral redistribution of blood volume. It has also been demonstrated that high intrathoracic pressure may play a role in the degree of bradycardia observed. Andersson et al. (1998) observed that the bradycardic effect was attenuated during periods of high intrathoracic pressure created at 85-100% of prone vital capacity. They concluded that high intrathoracic pressure reduced venous return and thus attenuated the development of diving bradycardia. Because there appears to be a relationship between venous return and the magnitude of diving bradycardia observed, manipulating factors that alter venous return (post-exercise hypotension, lower body pressure) may alter the bradycardic response.

Thus, the purpose of this study was to investigate the influence of cardiac filling on the diving reflex. Specifically, the study was undertaken to examine the interaction of the

parasympathetic response caused by facial immersion and the cardiovascular challenges created by the experimental conditions of modified venous return.

B) ***Hemodynamic mechanisms during post-exercise thermal recovery***

While the hemodynamics of exercise are well characterized, very little is known about the recovery period. It is the recovery period where episodes of post-exertional syncope are common and thus warrants further understanding of the cardiovascular mechanisms involved during resting exercise recovery.

Recovery from exercise presents many conflicting influences on the cardiovascular system. Kenny & Neidre (2002) have observed a post-exercise increase in esophageal temperature that is directly related to the intensity of exercise suggesting that blood temperature may facilitate a persistent thermoregulatory stimulus on the cardiovascular system. In addition to the influence of temperature during recovery, many studies have observed the phenomenon of post-exercise hypotension after intense exercise (Kenny & Neidre, 2002, MacDonald et al., 2000, 1999; Coats et al., 1989;). After exercise there are profound changes in the mechanisms that regulate and determine mean arterial pressure resulting in hypotension that is both vascular and neural in origin (Halliwill, 2001; Halliwill et al, 2000; Halliwill et al, 1996). Piepoli et al (1993) suggested there is persistent peripheral vasodilation that may cause pooling of warm blood and thus trap heat in the previously active muscle. This trapping of warm blood in conjunction with reduced skin blood flow and sweating during inactive recovery, would result in a time dependent transfer of heat from muscle to the core thus resulting in the observed prolonged elevation in esophageal temperature (Kenny & Neidre, 2002). The combined effects of persistent neural and vascular phenomena as well as the seated posture with dependent lower extremities and no muscle pump results in significant venous

pooling of blood (Halliwill, 2001; Kenny & Neidre, 2002; Kilgour et al., 1993). The accumulation of blood in the venous capacitance system undoubtedly has transient deficits on return over output, thus potentially compromising mean arterial pressure (Kilgour et al., 1993). The decrease in filling pressure of the heart during inactive recovery is sensed by cardiopulmonary baroreceptors and thus compromises skin blood flow; which is known to be on the efferent arm of the baroreflex (Johnson, 1986). Therefore if skin blood flow is compromised secondary to a venous pooling induced baroreflex, post-exercise heat loss is compromised. Thus, the question remains: how might the reversal of venous pooling using lower body positive pressure (LBPP) influence the decline in esophageal temperature? If esophageal temperature declines at a greater rate with LBPP, was the heat loss facilitated through increases in skin blood flow? Thus, this study will examine the hemodynamic mechanisms involved with the post-exercise heat loss response during resting seated recovery.

1.1 Rationale

A) Despite the rapid fall in cardiac output associated with the diving reflex, mean arterial pressure must still be maintained. Work by Andersson et al. (1998) showed an attenuation of diving bradycardia with high intrathoracic pressure which tends to reduce venous return and thus cardiac filling. It was also suggested by Arnold & Nadel (1993) that reduced cardiac filling associated with exogenous heat stress also attenuated the diving reflex. Thus, the rationale is that by using techniques known to alter cardiac filling, the reflex response observed will be altered.

B) It is known that a baroreceptor mediated reduction in skin blood flow and significant venous and muscle pooling appear to be contributing factors in the prolonged elevation in the post-exercise esophageal temperature. The combined effects of persistent neural and vascular phenomena

as well as the seated posture with dependent lower extremities and no muscle pump results in significant venous pooling of blood (Halliwill, 2001; Kenny & Neidre, 2002; Kilgour et al., 1993). Thus, using lower body positive pressure to facilitate the reversal of venous pooling and baroreceptor unloading seen during inactive recovery, it is a reasonable postulate that baroreceptor mediated increases in skin blood flow will accelerate the decline in esophageal temperature.

1.2 Hypotheses

General hypothesis of the thesis

It is hypothesized that under conflicting cardiovascular and thermoregulatory stimuli (facial immersion, postexercise) mechanisms that promote the maintenance of mean arterial pressure may override thermoregulatory responses.

Specific hypotheses of the experiments

A) It is hypothesized that reduced cardiac filling as a result of lower body negative pressure and post-exercise hypotension will attenuate the reflex changes to heart rate, skin blood flow and mean arterial pressure normally induced by cold water facial immersion.

B) It is hypothesized that reversal of venous pooling using LBPP will restore pre-exercise hemodynamics and potentially facilitate increase in skin blood flow, while maintenance of venous pooling using LBNP will exacerbate postexercise hemodynamics and compromise skin blood flow.

1.3 Statement of the problem

A) In an effort to better understand the mechanism of the human diving response and the cardiovascular controls by which it is governed, this study will examine the effect of manipulating cardiac filling on the responses observed.

B) At present, very little is known about blood pressure control and thermal responses during recovery from exercise. Thus, this experiment will be designed to address the cardiovascular and thermal mechanisms at play during exercise recovery.

1.4 Objectives

A) To examine the effect of various conditions of modified venous return (LBPP, LBNP, Post-exercise hypotension) on the human diving response.

B) To examine the effect of lower extremity blood pooling using LBNP and LBPP on the post-exercise hemodynamic and thermal response.

1.5 Relevance

A) This experiment will add one of the few remaining pieces of the puzzle regarding the mechanism of the human diving response. Facial immersion in cold water is both a brain stem neurological test and a bedside intervention for supraventricular tachycardia and thus may better our understanding of the pathways involved with cardiovascular control.

B) While thermoregulatory responses during exercise are well characterized, the cardiovascular mechanisms responsible for heat loss during seated recovery are scarce. Perhaps this experiment will better our understanding of venous pooling in the post-exercise heat loss response.

1.6 Delimitations

The results of these experiments will not be generalized to the entire population as the group being studied are young healthy male university students with no known pathologies. Secondly, females are not included as their cardiovascular responses to recovery from exercise are clearly unique as demonstrated by Carter et al. (2001).

1.7 Limitations

A) The neural responses and central hemodynamics of the response are speculative based on what has already been established in other studies. Thus, without direct measures of sympathetic activity and cardiac pressure-volume relationships, the conclusions are based on previously established mechanisms and observations of heart rate, skin blood flow, and mean arterial pressure.

B) While it is has already been established that pooling of blood in the previously active musculature and venous pooling occurs post-exercise, this study will not incorporate muscle blood flow measures. Thus, any conclusions made on muscle blood flow as a result of manipulation by lower body pressure would be speculative or based on previous investigations.

CHAPTER 2

REVIEW OF LITERATURE

2.1 *Introduction to human thermoregulation*

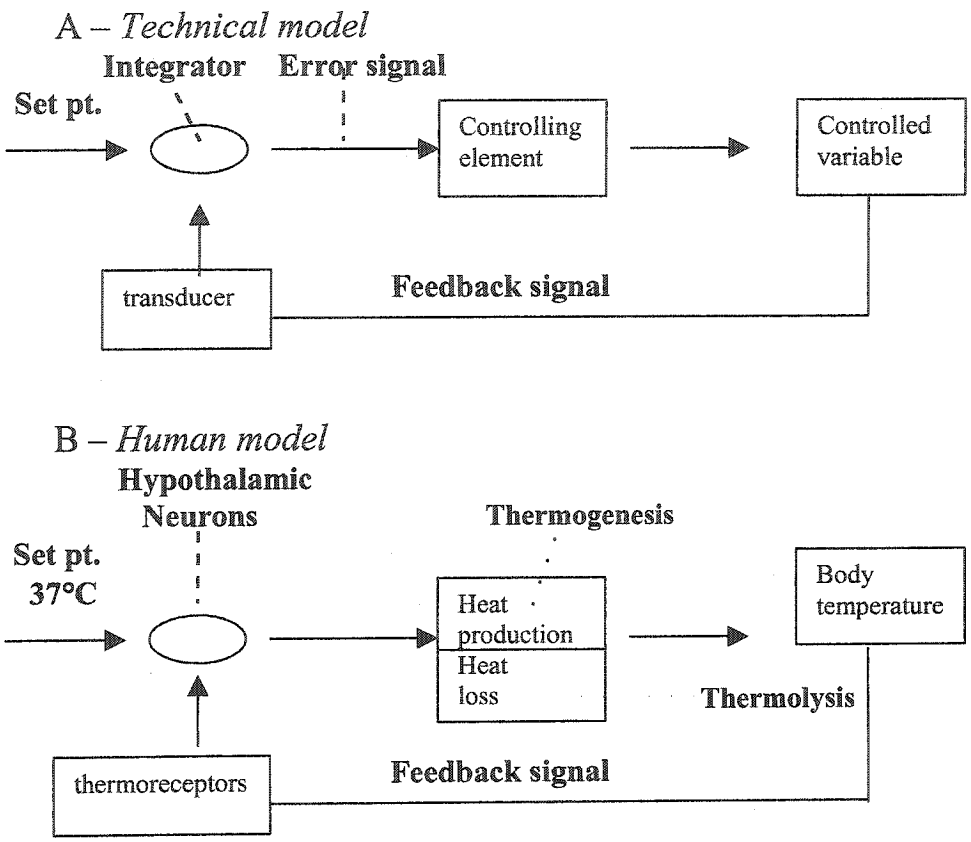
The human body constantly adapts to environmental stimuli such as air currents, air temperature, humidity and barometric pressure to maintain a set-point internal temperature (T_C) of 37°C. Fluctuations from this set point may also occur as a result of metabolic, mechanical (exercise) and/or endocrine actions (Segar & Moore, 1968; Huether & McCance, 2000;). Johnson (1998), suggested that the body aims to remain within 0.6°C of this value.

Deviation from this "set-point" can trigger two major actions that help defend ideal internal temperature. When the body is subjected to cold stress the process of thermogenesis occurs where actions that facilitate heat production are initiated (I.e. shivering, increased metabolism, and vasoconstriction). Conversely, when the body is exposed to heat stress the process of thermolysis facilitates heat loss through sweating, vasodilation and decreased metabolism (Levine, 2000; Armstrong, 2000).

The homeostatic mechanism that defends the body's ideal temperature is analogous to a control system commonly used in the field of engineering. Such control systems make use of negative feedback to maintain a desired variable within a specific range. This negative feedback control system occurs through the hypothalamus in humans.

A typical control system features a *set-point, an integrator (or error detector),* a *controlling element,* a *controlled variable* and a *feed back signal transducer* (Levine, 2000). Each of these components is analogous to a part of our thermoregulatory system as illustrated in the diagram below.

Fig. 1



(Levine, 2000)

The process of reading thermal signals can occur through peripheral thermoreceptors such as those located in the face, or central thermosensitive neurons in hypothalamus which can detect changes in circulating blood temperature (Parfrey & Sheehan, 1975; Conn & Freeman, 2000). Upon reading the error differential between the set-point and the incoming stimulus, appropriate sympathetic responses are initiated such as changes in vasomotor contractile status, metabolic rate, and sweating or shivering responses.

The above is a brief overview of how thermoregulation is controlled, however each of the responses to thermal stimuli (I.e. vasodilation, vasoconstriction) have

individual mechanisms by which they occur. The mechanisms pertinent to the field of thermoregulation and cardiovascular homeostasis will be discussed in the following analysis of the literature.

2.2 *Baroreceptor modulation of heart rate and blood pressure*

Blood pressure in general is controlled by many mechanisms including changes in cardiac output, alterations in peripheral vascular resistance as well as neuroendocrine reflexes. Baroreceptors are small pressure sensing structures located in the carotid sinus and aortic arch (arterial baroreceptors) as well as in the atria, ventricles and pulmonary vessels (cardiopulmonary baroreceptors). Impulses received by receptors in the aortic arch travel up the vagus nerve to the nucleus tractus solitarius (NTS) in medulla while the carotid arch receptors act through the sinus nerve up to the glossopharyngeal nerve and then are received by the nucleus tractus solitarius (Berne and Levy, 2001). Stimulation of the NTS (baroreceptor loading) causes a depressor effect where by sympathetic nerve impulses to the peripheral blood vessels are inhibited.

Baroreceptor loading results in a decrease in vasoconstrictor tone, which in turn leads to vasodilation. Simultaneously, an increase in vagal activity results in a reduced heart rate. Conversely, reduced NTS stimulation (baroreceptor unloading) facilitates vasoconstriction and an increase in heart rate (Tripathi et al, 1989). The process of vasodilation and reduced heart rate combine to lower blood pressure, whereas vasoconstriction and increased heart rate raise blood pressure.

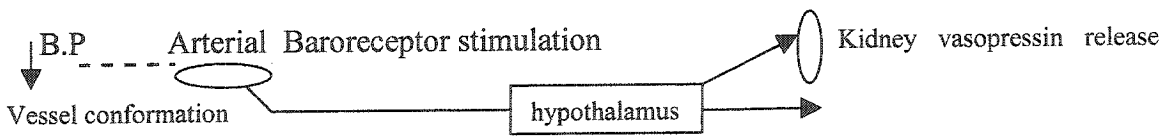
The significance of blood pressure and heart rate in this study is that adequate pressure must be maintained during orthostatic challenge (Ie. During LBNP and inactive

exercise recovery) to prevent presyncope or syncope due to inadequate blood supply to the brain (Butler et al, 1992). The facial immersion component of the study also presents the cardiovascular centers with a challenge to maintain blood pressure because it stimulates a reduction in heart rate during periods of reduced or enhanced venous return.

2.3 *The role of baroreceptors in neuroendocrine reflexes*

Although the baroreceptors are frequently investigated from a neural point of view due to their neurally mediated baroreflexes, their role in facilitating endocrine responses has only been investigated. One of the major neuroendocrine responses facilitated by baroreceptors is the release of vasopressin. Vasopressin is a potent vasoconstrictor that is released to defend arterial pressure during low blood pressure and hemorrhage (Shen et al, 1991). While osmoreceptors respond to changes in osmolality, baroreceptors respond to changes in blood pressure and volume to release vasopressin. It is unclear at this time the roles of arterial and cardiopulmonary baroreceptors in blood pressure-volume control of vasopressin release (Share & Schneider, 2000).

Norsk et al, (1993) noted that unloading of arterial baroreceptors seems to be a prerequisite for inducing increases in plasma arginine vasopressin during low body negative pressure (LBNP). This has been supported by many other investigations that have shown that selective unloading of cardiopulmonary baroreceptors during low levels of LBNP without changes in arterial pressure did not induce an increase in arginine vasopressin release (Goldsmith et al, 1982; Leimbach et al, 1984; Norsk, 1986; Norsk et al, 1986). **Fig. 2**



2.4 *Cardiovascular responses to the application of lower body negative and positive pressure*

Manipulating pressure gradients in the body can result in changes in central venous pressure, mean arterial pressure and cardiac output. Lower body negative pressure (LBNP) has been used extensively to study reflex responses to venous pooling and to test orthostatic intolerance in humans (Halliwill et al, 1998). LBNP results in a reduced cardiac filling pressure and unloads cardiopulmonary and arterial baroreceptors (Tripathi et al, 1984). Recent work by Hisdal et al. (2001, 2002) noted that cardiopulmonary baroreceptors are engaged during LBNP when there is a change in heart rate but no change in mean arterial pressure, suggesting that an increase in heart rate is sufficient to maintain blood pressure. Interestingly, at the onset of mild LBNP Hisdal et al. (2002) observed a transient change in MAP suggesting that only at the onset of LBNP are arterial baroreceptors activated and upon activation of compensatory mechanisms MAP is returned to pre-LBNP values.

LBNP at –40 to –50 mmHg in the supine position has been shown to reduce cardiac filling pressure due to local blood pooling in the legs. The body attempts to counteract the drop in filling pressure (during LBNP) by eliciting baroreflex-mediated vasoconstriction in skeletal muscle and skin (Zoller et al. 1972; Rowell et al. 1973). It has been reported more recently that such increases in forearm venomotor tone are proportional to the level of LBNP (Tripathi et al, 1984). Regional vasoconstriction during LBNP occurs because arterial pressure must be maintained by a fall in vascular conductance inasmuch as the fall in ventricular filling pressure restricts the ability to raise cardiac output (Escourrou et al, 1993). There is substantial research in agreement that

baroreceptor-unloading decreases skin blood flow (Rowell et al. 1973; Mack et al. 1988; Kellogg et al 1990).

The application of lower body positive pressure (LBPP) leads to an increase in both central venous pressure and mean arterial pressure through an enhanced gradient for venous return (Tripathi et al, 1984). Nishiyasu et al., (1998) examined the cardiovascular responses to LBPP in the supine and seated resting conditions. LBPP caused dramatic increase in stroke volume in the upright postion from resting to +25 mmHg. Interestingly stroke volume was maximized between +25 and+50 mmHg and declined at higher pressures. The decline in stroke volume at high levels of LBPP is thought to occur as a result of increased MAP which leads to increased total peripheral resistance and thus an increase in end-diastolic volume (Nishiyasu et al., 1998). In the supine position stroke volume did not change significantly with the addition of LBPP. The hemodynamics of LBPP in the upright position are particularly important for the facial immersion chapter of this study because it is important to understand the baseline status of cardiac filling before immersion is performed.

Early work by Bevergard et al. (1966) using lower body positive pressure (LBPP) of 40 mmHg as a means of increasing venous return demonstrated reflex forearm vasodilation via low-pressure (or cardiopulmonary) baroreceptor loading. In a study by Shi et al. (1993) it was found that the hemodynamic responses of the human to progressive increases in LBPP while at supine rest may be as a result of two different stimuli. An initial stimulus of LBPP occurs between 0 and 20 Torr (1 Torr = 1 mmHg) LBPP and appears to be a result of translocation of blood volume from the lower body to

the thorax. It was found that LBPP above 20mmHg increases blood flow to the forearm (Shi et al, 1993).

In many cases, studies in the literature used the supine position or failed to mention what body position was used when administering LBNP/LBPP. It is only recently that the cardiovascular responses to LBNP/LBPP in the upright seated position are being investigated. It presents a more realistic challenge to the cardiovascular system by adding an additional gravitational pumping gradient. The lower body pressures reported in the literature while supine (as great as -40-50mmHg) would result in syncope in the seated position.

2.5 The physiological responses to cold stimulation, pressor response, and facial immersion

Cold stimulation of the face is a noninvasive method of activating trigeminal brain stem cardiovagal and sympathetic pathways (Hilzl et al, 1999). It has been shown that cooling of the face produces systemic cardiovascular responses, such as an increase in blood pressure and a decrease in heart rate, as a result of a reflex influence from the cold stimulation of the facial trigeminal nerve (Leblanc & Mercier, 1992). However, the dive reflex, which will be initiated by apneic facial immersion in this study elicits a more profound bradycardia and involves breath holding (Abboud & Eckstein, 1966; Anderson et al, 1988). It has also been demonstrated that facial immersion is consistently temperature dependent such that lower immersion temperatures result in greater bradycardia (Parfrey & Sheehan, 1975).

The cold pressor test is used as a clinical and experimental tool commonly used to induce a rapid and substantial blood pressure increase (Durel et al, 1993). In the forehead cold pressor test, increases in both systolic and diastolic blood pressure and a small decrease in heart rate occur (Abboud & Eckstein, 1966; Anderson et al, 1988). The cold stimulation also induces peripheral vasoconstriction (Hilzl et al, 1999; Mannino & Washburn, 1987). Such stimulation therefore combines to activate the peripheral sympathetic and cardiac parasympathetic nervous system (Andersson et al, 2000; Hilzl et al, 1999).

The human diving response is initiated by apnea and augmented by facial immersion in cold water (Gooden, 1994). Like that of facial cold stimulation alone, the reflex is characterized by significant bradycardia and peripheral vasoconstriction. While it has been suggested that adequate cardiac filling is a requirement for the development of the diving response, it has yet to be demonstrated directly. It is unclear at this time how the response is changed during altered venous return and thus cardiac filling. Only a few studies have implicated reduced venous return in the production of bradycardia. Arnold and Nadel (1993) demonstrated that diving bradycardia can be attenuated subsequent to an increased thermal load induced by exogenous heating in 68°C ambient heat. They contended that the attenuation of diving bradycardia occurs as a result of reduced cardiac filling due to peripheral redistribution of blood volume. It has also been demonstrated that high intrathoracic pressure may play a role in the degree of bradycardia observed. Andersson et al. (1998) observed that the bradycardic effect was attenuated during periods of high intrathoracic pressure created at 85-100% of prone vital capacity. They concluded that high intrathoracic pressure reduced venous return and thus attenuated the

development of diving bradycardia. Because there appears to be a relationship between venous return and the magnitude of diving bradycardia observed, manipulating factors that alter venous return (post-exercise hypotension, lower body pressure) may alter the bradycardic response.

The facial immersion chapter will address this question by examining the responses to facial immersion under conditions of altered venous return (LBNP, LBPP and post-exercise hypotension).

2.6 *Thermoregulatory control of skin blood flow*

Skin blood flow (SkBF) in humans occurs due to reflex responses as well as local factors. In humans, cutaneous blood flow is mediated through two sympathetic pathways: a noradrenergic vasoconstrictor system and a vasodilator system of unknown transmitter (Kellogg et al, 1989).

In a resting human, the response in skin blood flow (SkBF) to heat stress is characterized by an internal temperature threshold, beyond which the rise in SkBF per degree Celsius is fairly steep (Johnson, 1986). In thermally neutral environments, skin receives ~5-10 percent of cardiac output, whereas in conditions of heat stress, SkBF can reach 50-70 percent of cardiac output (CO), approaching 8 liters per minute (Crandall et al, 1996).

Cutaneous arterioles under tonic control of sympathetic vasoconstrictor fibers and arterioles are also regulated by a unique vasodilator system, which is responsible for 95 to 100 percent of the total increase in skin blood flow during heat stress (Rowell, 1986). For the purposes of describing the control of SkBF, the skin surface can be divided into

two regions: 1) acral or glaborous (i.e., hands, feet, nose, and ears) and 2) non-acral or non-glaborous (i.e., head, limbs, and trunk). In acral regions, cutaneous arterioles are innervated only through noradrenergic sympathetic nerves (Johnson, 1986). Thus, it follows that all thermoregulatory and nonthermoregulatory reflexes in the acral skin regions are mediated by adjustments in active vasoconstrictor tone. Non-acral areas contain a much more complex system for controlling SkBF. Efferent neural control of SkBF to these areas is accomplished via two sympathetic neural pathways: a noradrenergic vasoconstrictor system (both α_1- and α_2-receptors) and a separate active vasodilator system still under investigation (Freedman et al, 1992; Frank et al, 1997; Stephens et al, 2001).

The amount of SkBF supplied to a given area is mediated by two factors: 1) local factors (i.e., local warm/cold sensation, pressure responses, pressor response etc.) and 2) reflex control factors (e.g., internal/metabolic heat production heat.). A local factor that affects cutaneous circulation is a direct heating of the blood vessels themselves; however, the mechanisms for the vascular effects of local temperature are not yet well defined (Pergola et al. 1993). As stated by Johnson et al. (1986), local cooling potentiates, and heating weakens, the contractile response of vascular smooth muscle to norepinephrine and other constrictor agonists, apparently by changing the affinity of α_2-andrenergic receptors. Recent research, involving local heating and cooling and observing the subsequent cutaneous vascular responses has suggested a prominent role for postjunctional α_2-adrenoreceptors (Freedman et al, 1992). Local cooling has shown to enhance the affinity of α_2-adrenoreceptors for norepinephrine and depress the function of other elements involved in vascular smooth muscle function. Conversely, the process of

local heating is known to induce nitric oxide release which contributes to the active vasodilation phenomenon (Kellogg et al, 1999; Shastry et al, 2000)

2.7 Sweating

Increasing internal temperature leads to an increase in sweat rate. This event occurs after the release of acetylcholine (ACh) from sudomotor nerves innervating muscarinic receptors (Pappano, 1998). In addition to rising internal temperature as a result of exogenous heat stress or exercise, sweating has also been shown to be modulated by nonthermal factors such as central command, muscle mechano/metaboreceptor activation and baroreflexes (Mack et al., 1995; Yamazaki et al., 1996; Kondo et al., 1999). However, independent roles of these factors are unclear.

During heat stress increases in sweating can be due to either 1) an increase in the density of activated sweat glands or 2) as a result of an increase in sweat output per gland, or 3) a combination of the two (Kondo, 2001). A study by Kondo et al. (2001) showed that changes in forearm sweating rely on both the number of activated sweat glands and sweat output per gland during the initial periods of exercise and passive heating, whereas further increases in sweat rate are attributed to increases in sweat output per gland only.

2.8 Influence of central command on the cardiovascular system

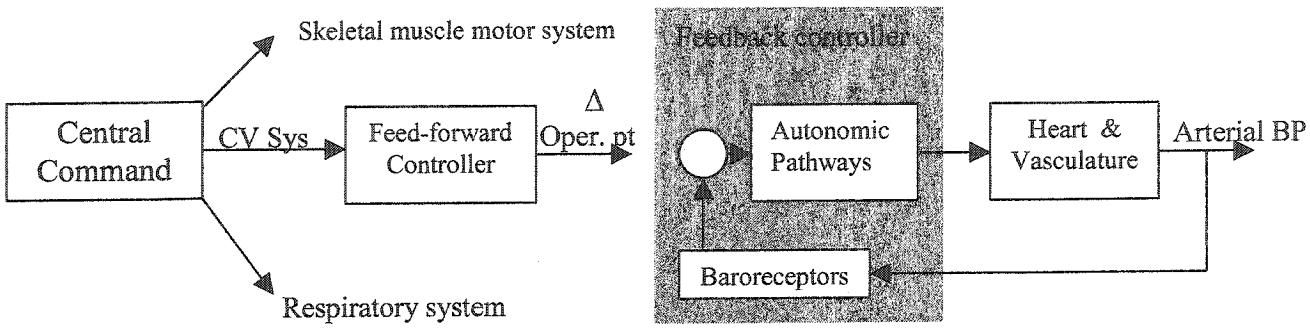
When examining the role of central command on the cardiorespiratory system it is important to note the close proximity of the locomotor brain centers and the cardiorespiratory centers of the medulla. While there are many areas of the brain implicated in motor function the area thought to have a significant effect on the circulatory and respiratory centers is the pre-motor cortex component of the cerebral cortex. This area is associated with the generation of motor signals in voluntary movement. The significance of the pre-motor cortex is that it projects into the medullary reticular formation which is one of the areas involved in outflow controlling cardiorespiratory activity (Waldrop et al. 1996).

According to Rowell (1980), the central hypothesis of central command is that it acts through cortical and motor systems "to set the basic patterns of effector activity which are in turn modulated by baroreceptors, muscle mechanoreceptors and muscle chemoreceptors as error signals may develop". While the evidence that central command generates effector activity is plentiful, the mechanisms by which the patterns of activity are modulated remain less clear. Two major questions to address are where and how are the signals integrated in the CNS? And, which of the peripheral sensors are dominant in effecting a response during central command stimulation?

During exercise in the rat model, central command appears to suppress the baroreceptor reflex. Activation of the posterior hypothalamic neurons that produce locomotor and cardiorespiratory responses appropriate for exercise exerts a depressive effect on the baroreceptor reflex (Bauer et al., 1988). This depressive effect is thought to allow for prolonged high systolic pressures during dynamic exercise.

Fig. 3

Scheme for feed forward and feedback control during exercise:



Adapted from Houk (127) reproduced with permission by Rowell (268) p. 793 Handbook of Physiology

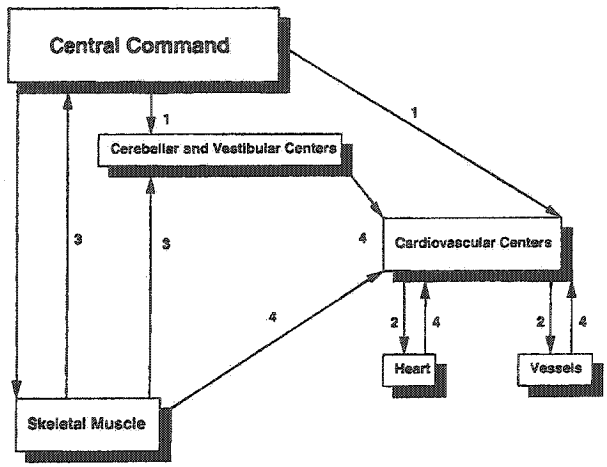
2.9 Cessation of central command during exercise recovery

At the cessation of exercise, thermoregulatory responses such as sweating and skin blood flow may be subject to nonthermoregulatory responses. Carter et al. (2002) suggested this based on their observation that skin blood flow and sweating decrements during recovery are attenuated with the presence of active recovery thus implicating central command and the muscle pump.

It is well known that skin blood flow is subject to non–thermoregulatory baroreceptor reflexes (Johnson, 1986). Baroreceptor engagement is dependent on the signals received under a given hemodynamic status (ie. hypertensive, hypotensive, posture). During exercise recovery, hemodynamics experience a rapid transition upon the removal of central command. This rapid change suggests a possible role for the baroreceptors in maintaining skin blood flow and sweating during active or inactive recovery, however their contribution is not completely understood. This study will

attempt to evaluate the relative roles of central command and skeletal muscle pump engagement in maintaining skin blood flow and sweating during intense exercise recovery.

Fig. 4 *(From DiCarlo & Bishop, 1999)*

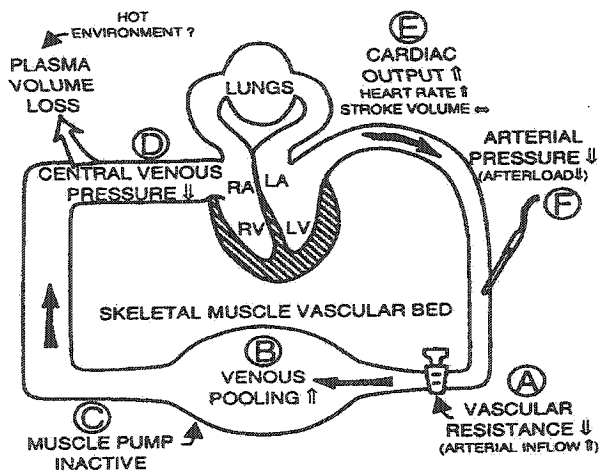


3.0 Hemodynamics during resting recovery from dynamic exercise

When dynamic exercise is stopped and inactive recovery occurs in the upright posture, MAP decreases rapidly in the first 1-2 minutes (Carter et al., 1999). Similarly stroke volume and cardiac output fall in parallel. In contrast however, total peripheral resistance (TPR) increases towards pre-exercise levels. Despite increases in TPR, thoracic impedance values indicate a decrease in central blood volume during inactive recovery compared to that of active recovery modes (Carter et al., 1999, 2002). It is thought that decrements in central blood volume during inactive recovery are associated with the accumulation of blood in the venous capacitance system of the lower extremities in the absence of the muscle pump (Kilgour et al, 1993; Halliwill, 2001; Carter et al., 1999). In addition to venous pooling, persistent muscle vasodilation (Piepoli et al., 1993)

and the remaining thermal influence as a result of the dynamic exercise ultimately lead to reduced pre-load (Kilgour et al., 1993). Despite a reduction in pre-load, some investigations have demonstrated greater inotropic activity during the first 5-10 minutes of recovery (Kilgour & Sellers, 1990). The combined effects of warm blood stimulating the SA node (Gorman and Proppe, 1984), and decreased pre-load induced stretch will result in increased heart rate. The increased heart rate and contractility as a result of enhanced adrenergic sensitivity (Dimsdale et al., 1984) lead to a post-exercise cardiac output that is actually equal to or exceeds pre-exercise values (Kilgour et al., 1993).

Fig. 5 *(from Halliwill, 2001)*



CHAPTER 3

METHODOLOGY

3.0 Measurement techniques

A) The reflex response to apneic facial immersion involves a reduction in heart rate, peripheral vasoconstriction and a rise in mean arterial pressure. Thus, the following parameters will be recorded.

Heart rate – Recorded from lead 5 on a Quinton 400B electrocardiogram (Quinton Instruments Company, Seattle,WA,USA)

Mean arterial pressure – will be estimated from the integration of a non-invasive recording of blood pressure at the middle digit of the left hand (Finapres 2300, Ohmeda, Madison, WI, USA) fixed at heart level (the third intercostal space). The Finapres system is based on the volume clamp method (dynamic unloaded arterial wall principle) introduced by Penaz. This method has proven to provide accurate measures of MAP in other studies examining facial immersion and exercise (Andersson et al., 1998, 2000, 2002).

Skin blood flow – will be estimated using laser-Doppler velocimetry (PeriFlux System 5000, Main control unit; PF5010 LDPM, Function unit; Perimed AB, Stockholm, Sweden) at the left mid-anterior forearm and at the level of the distal phalanx of the thumb. The laser-Doppler flow probes (PR 401Angled Probe, Perimed AB, Stockholm, Sweden) will be taped to cleaned skin, in an area which does not appear by visual inspection overly vascular and from which consistent readings are noted (Mack, 1998). The Perimed system determines flow only where as other systems can distinguish between blood volume and velocity changes.

B) The following recordings will be taken in the subsequent experiments examining hemodynamic and thermal responses of exercise recovery:

Skin blood flow and mean arterial pressure will be recorded as described previously.

Heart rate – will be recorded using the Polar Heart Rate system which involves a band attached to chest at the inferior crest of the sternum, where by heart rate is transmitted and stored on a nearby watch that accompanies the device.

Esophageal temperature - central body temperature will be monitored continuously using a pediatric esophageal temperature probe (Mon-a-therm®, Mallinckrodt Medical, St-Louis, USA) inserted through the nares to a depth one-fourth of the standing height of the subject, whereby the tip of the thermocouple is estimated to be at the level of the left atrium (Mekjavic & Rempel, 1997).

Skin temperature – will be recorded at 11 sites using heat flow sensors (Concept Engineering, Old Saybrook, CT, USA, model FR-025-TH44018-6). The area-weighted mean skin temperature ($\bar{T}_{sk}$) will be estimated by calculating the weighted mean value whereby the following regional percentages are assigned: head 6%, upper arm 9%, forearm 9.5%, finger 2%, chest 19%, upper back 9.5%, lower back 9.5%, anterior thigh 10%, posterior thigh 10%, anterior calf 9.5%, and posterior calf 9.5%. Temperature data will be collected and digitized (Hewlett-Packard data acquisition module, model 3497A) at 5-s intervals, displayed graphically in real time and stored on hard disk (Hewlett-Packard, model PC-312, 9000).

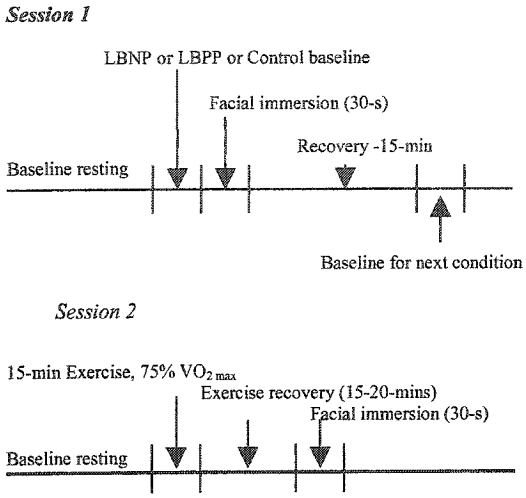
Cardiac output – Will be determined using the Defares/exponential method of CO_2 rebreathing (Defares, 1958) on the Medgraphics metabolic system. This technique

involves analyzing the exponential rise in P_{ET} CO_2 as the subject rebreathes 4% CO2, 35% O_2 and the balance N_2. This Fick indirect CO_2 rebreathing method for determining cardiac output has been tightly correlated with both Doppler-derived aortic blood flow cardiac output measurements (Hadjis et al., 1995) as well with direct Fick and indicator dilution methods (Cerretelli et al, 1966; Inman et al., 1985; Collier, 1956).

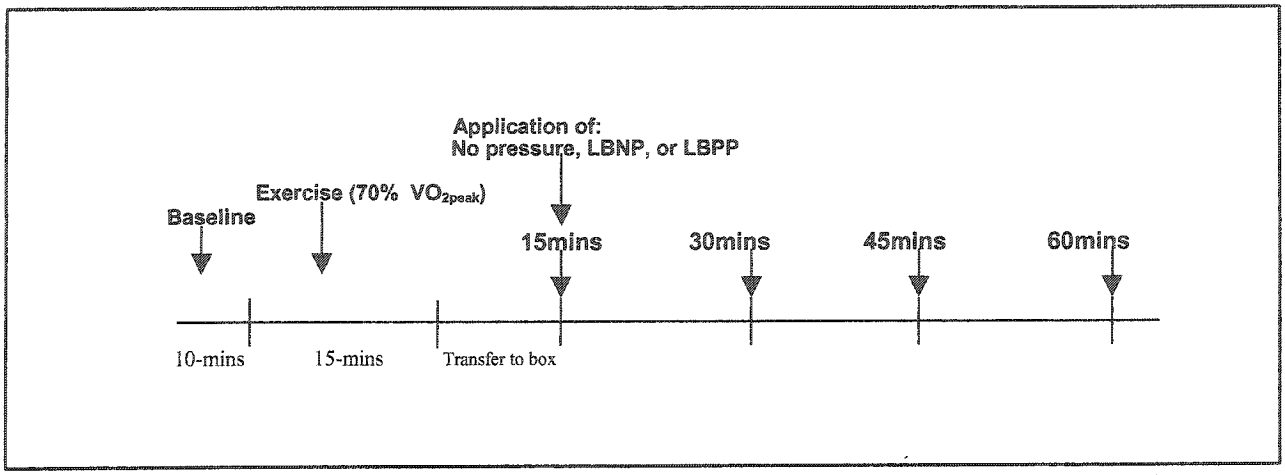
3.1 General overview of the protocols

A) A total of four trials will be performed with the subjects being required to come to the laboratory on two separate days. The Control (no pressure), LBNP (-20mmHg) and LBPP (+40mmHg) immersion conditions will be performed in one session, while the Post-exercise hypotension immersion will be performed on a separate day to avoid the influence of exercise on the other immersion conditions. Each immersion in the first session will include a resting baseline, followed by the application of the condition (Ie LBNP or LBPP). Upon achieving stable cardiovascular recordings, the subjects will perform a 30-s apneic facial immersion such that the forehead and chin are submerged in approximately 6.0°C water. The subjects will then undergo an approximately 15-min recovery period. This recovery period is of greater length than that used by Arnold et al., (1991) whose subject's performed multiple vagal maneuvers.

The exercise trial will consist of a baseline resting recording, followed by 15-mins of treadmill exercise at an intensity of 70% of their pre-determined VO_{2max}. After exercise the subjects will be place in the seated position until, esophageal temperature is stable and skin temperature has return to pre-exercise values. Facial immersion will then be performed as described previously. See protocol diagram below.



B) This protocol will require that the subjects come to the laboratory on 3 separate days. Subjects will perform 15-mins of cycle ergometer exercise at 70% of their pre-determined $VO_{2\,max}$ and then be transferred to the lower body pressure box and positioned in the upright posture for recovery. Upon being positioned in the box the subject will then recover for 60-mins under 1 of 3 conditions: 1) +45 mmHg 2) –20 mmHg or 3) No pressure. Skin blood flow, MAP, HR, esophageal temperature and skin temperature will be recorded continuously, while measures of cardiac output will occur every 15-mins.


Application of:
No pressure, LBNP, or LBPP
Exercise (70% VO_{2peak})
Baseline
15mins
30mins
45mins
60mins
10-mins
15-mins
Transfer to box

PART TWO:

RESULTS OF THE THESIS

FINAL ACCEPTED VERSION
(JAP-01140-2002.R3)

Cardiovascular responses to apneic facial immersion during altered cardiac filling

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Running Head: Diving bradycardia and cardiac filling

ABSTRACT

The hypothesis that reduced cardiac filling, as a result of lower body negative pressure and post-exercise hypotension, would attenuate the reflex changes to heart rate (HR), skin blood flow (SkBF) and mean arterial pressure (MAP) normally induced by facial immersion was tested. The purpose of this study was to investigate the cardiovascular control mechanisms associated with apneic facial immersion during different cardiovascular challenges. Six subjects randomly performed 30-s apneic facial immersions in 6.0 ± 1.2 °C water under: 1) –20mmHg lower body negative pressure (LBNP); 2) +40mmHg lower body positive pressure (LBPP); 3) during a period of post-exercise hypotension (PEH); and 4) normal resting (Control). Measurements included SkBF at 1 acral (distal phalanx of the thumb) and 1 non-acral region of skin (ventral forearm), HR and MAP. Facial immersion reduced HR and SkBF at both sites and increased MAP under all conditions ($P<0.05$). Reduced cardiac filling during LBNP and PEH significantly attenuated the absolute HR nadir observed during the control immersion ($P<0.05$). The LBPP condition did not result in a lower HR nadir than control but did result in a nadir significantly lower than that of the LBNP and PEH conditions ($P<0.05$). No differences were observed in either SkBF or MAP between conditions, however, the magnitude of SkBF reduction was greater at the acral site than at the non-acral site for all conditions ($P<0.05$). These results suggest that the cardiac parasympathetic response during facial immersion can be attenuated when cardiac filling is compromised.

Key words: Diving response, bradycardia, skin blood flow, lower body pressure, blood pressure.

INTRODUCTION

The human diving response is initiated by apnea and is augmented by facial immersion in cold water (14). This reflex response is characterized by a reduction in heart rate through vagus nerve action and by α-adrenergic vasoconstriction in selected vascular beds (2, 6, 14). Superficial cold receptors that are innervated by the ophthalmic branch of the trigeminal nerve enhance the cardiovagal activity involved in the response (18, 22, 31).

While the mechanism of diving bradycardia is known to be parasympathetically mediated, it is unclear at this time how the response is changed during altered cardiac filling. Only a few studies have implicated reduced cardiac filling in the attenuation of bradycardia. Arnold and Nadel (5) demonstrated that diving bradycardia can be attenuated subsequent to an increased thermal load induced by exogenous heating in 68°C ambient heat. They contended that the attenuation of diving bradycardia occurs as a result of reduced cardiac filling due to peripheral redistribution of blood volume. It has also been demonstrated that high intrathoracic pressure may play a role in the degree of bradycardia observed. Andersson et al. (1) observed that the bradycardic effect was attenuated during periods of high intrathoracic pressure created at 85-100% of prone vital capacity. They concluded that high intrathoracic pressure occluded venous return impeding cardiac filling and thus attenuated the development of diving bradycardia. While it has been suggested that adequate cardiac filling is a requirement for the development of the diving response, it has yet to be demonstrated directly. Because there appears to be a relationship between cardiac filling and the magnitude of diving bradycardia observed, manipulating factors that alter cardiac filling (post-exercise hypotension, lower body pressure) may alter the bradycardic response.

Cardiac filling can be altered via different techniques. Application of mild lower body negative pressure (LBNP) reduces cardiac filling pressure through venous pooling (30, 33) unloads cardiopulmonary baroreceptors (19, 20) and increases efferent sympathetic activity (7). During post-exercise hypotension (PEH) mean arterial pressure is reduced via both neural and vascular phenomena (15-17). PEH is thought to occur as result of venous blood pooling in the previously active musculature and its magnitude varies directly with the post-exercise elevation in esophageal temperature (8, 23). In the post-exercise hypotensive period removal of the muscle pump and the seated posture has transient deficits of return over output as blood accumulates in the venous capacitance system, thus compromising pre-load (15, 24). In contrast, lower body positive pressure (LBPP) creates a greater venous pressure gradient that tends to increase cardiac filling, load cardiopulmonary baroreceptors and inhibit efferent sympathetic activity (13).

Thus, the purpose of this study was to investigate the influence of cardiac filling on the diving reflex. Specifically, the study was undertaken to examine the interaction of the parasympathetic response arising from facial immersion and the simultaneous challenge created by the three experimental conditions of modified cardiac filling. It was hypothesized that reduced cardiac filling as a result of LBNP and PEH would attenuate the reflex changes to HR, SkBF and MAP normally induced by facial immersion.

METHODS

Subjects

Six healthy, physically active men volunteered and gave written consent to participate in this study. The study was approved by the Research Ethics Board of the University of Ottawa. Five to seven days before the experiments, maximal oxygen consumption ($\dot{O}_{2peak}$) was measured during a progressive treadmill protocol. The $\dot{O}_{2peak}$ data were used to select the submaximal workload for the experimental exercise phase of the study. Subjects were (mean ± SEM) 23 ± 1 years old, 176 ± 2 cm tall, weighed 71 ± 2 kg. Their mean maximal aerobic capacity was 58.0 ± 2.3 $ml \cdot kg^{-1} \cdot min^{-1}$.

Measurements

Heart rate (HR) was recorded continuously from pre-cordial lead 5 on a Quinton 4000B electrocardiogram (Quinton Instruments Company, Seattle, WA, USA). Mean arterial pressure (MAP) was estimated from the integration of a non-invasive recording of blood pressure at the middle digit of the left hand (Finapres 2300, Ohmeda, Madison, WI, USA) fixed at heart level (the third intercostal space). The Finapres system is based on the volume clamp method (dynamic unloaded arterial wall principle) introduced by Penaz. This method has proven to provide accurate measures of MAP in other studies examining facial immersion (1-3). These blood pressure data were recorded and stored continuously at 5-s intervals.

Skin blood flow (SkBF) was estimated using laser-Doppler velocimetry (PeriFlux System 5000, Main control unit; PF5010 LDPM, Function unit; Perimed AB, Stockholm, Sweden) at the left mid-anterior forearm and at the level of the distal phalanx of the

thumb. The laser-Doppler flow probes (PR 401Angled Probe, Perimed AB, Stockholm, Sweden) were taped to cleaned skin, in an area which did not appear by visual inspection overly vascular and from which consistent readings were noted (26).

During the exercise component of the study body temperature was recorded from several sites. Thus, central body temperature (esophageal temperature, T_{es}) was monitored continuously using a pediatric esophageal temperature probe (Mon-a-therm®, Mallinckrodt Medical, St-Louis, USA) inserted through the nares to a depth one-fourth of the standing height of the subject, whereby the tip of the thermocouple is estimated to be at the level of the left atrium (27). Skin temperature was recorded at 11 sites using heat flow sensors (Concept Engineering, Old Saybrook, CT, USA, model FR-025-TH44018-6). The area-weighted mean skin temperature ($\bar{T}_{sk}$) was estimated by calculating the weighted mean value whereby the following regional percentages were assigned: head 6%, upper arm 9%, forearm 6%, finger 2%, chest 19%, upper back 9.5%, lower back 9.5%, anterior thigh 10%, posterior thigh 10%, anterior calf 9.5%, and posterior calf 9.5%. Temperature data were collected and digitized (Hewlett-Packard data acquisition module, model 3497A) at 5-s intervals, displayed graphically in real time and stored on hard disk (Hewlett-Packard, model PC-312, 9000).

The lower body negative pressure (LBNP) and lower body positive pressure (LBPP) conditions were created by inserting the subject up to the hips in a pressure chamber, sealed with a neoprene skirt at the level of the iliac crest. The chamber was designed to permit creating both hyperbaric and hypobaric conditions about the lower body segments with the subject in an upright semi-seated position.

Experimental Protocol

Each subject performed a total of 4 experimental trials carried out in random order. The first experiment was conducted following a 36-hour period during which subjects were instructed to avoid physical activity and excessive stressors such as exposure to hot or cold temperatures, particularly during the period between awakening and experimentation and during transit from home to the laboratory. Further, they were asked to fast at least 4 h prior to experimentation, and water ingestion was permitted during this time.

Subjects were required to come to the laboratory for two experimental sessions at an interval of not less than 48 hours. During the first experimental session, the subjects performed facial immersion under the LBNP, LBPP and Control conditions in random order. Arnold et al. (4) had their subjects perform multiple vagal maneuvers on the same day and allowed a minimum 3-minute recovery interval between maneuvers. Thus, we feel that performing multiple immersions with the recovery interval described below that possible residual effects between conditions were avoided. In order to avoid the residual effects of exercise, the exercise trial was performed on a separate day. The order in which session one and two were carried out was also randomized. All trials were performed at an ambient temperature of 26°C. A schematic representation of the experimental timeline is presented in Figure 1.

Session 1 - Each condition began with a 5-min upright rest period during which baseline readings were taken (pre-condition baseline resting). The baseline resting period was carried out while the subject was in the pressure chamber in order to minimize the effect of posture across and within subjects for all measures. Subjects were then exposed

to either -20 mmHg LBNP, +40 mmHg LBPP or no lower body pressure (Control). Once the subject was positioned within the pressure chamber and all cardiovascular parameters had stabilized, a 30-s baseline reading was recorded. Stabilization occurred in less than 5-minutes for all subjects. After baseline values had been registered under each condition, subjects then performed a 30-s apneic facial immersion in cold water (6.0 ± 1.2 °C). The immersion time was pre-determined and has been used by other studies (3, 5, 6). The water-filled container was placed below the subject's chin such that total facial immersion including the forehead and chin was achieved by simple flexion of the neck. Facial immersions were performed during a mid-inspiratory breath hold and subjects were cautioned to avoid the Valsalva maneuver (5, 6). Recordings were continued for two minutes post-immersion and there was a 15-minute interval between the end of facial immersion and the commencement of the 5-min baseline period of the next condition. Thus there was a 20-minute interval between dives.

Session 2 - Subjects reported to the laboratory and were fitted with an esophageal thermocouple and the skin heat flow sensors before a 5-minute baseline recording of T_{es}, $\bar{T}_{sk}$, heart rate, skin blood flow and mean arterial pressure was performed. The subjects then performed 15-minutes of exercise on the treadmill at a work rate equivalent to 70% of their pre-determined maximal oxygen consumption. This intensity has previously been reported to be effective in eliciting post-exercise hypotension (23, 25). After exercise the subjects were seated in the upright position until $\bar{T}_{sk}$ returned to pre-exercise values and a plateau in elevated T_{es} was observed. That is, facial immersion was initiated when $\bar{T}_{sk}$ had returned to pre-exercise values, and when T_{es} and cardiovascular measures were

stable. The stabilization of $\bar{T}_{sk}$, T_{es} and cardiovascular measures occurred within 15-20 minutes post-exercise and was consistent with the results of Kenny and Neidre (23)

Data analysis

A 30-s resting average was calculated before any of the conditions were administered. The 30-s period between 60-30-s before facial immersion was used to calculate average baseline values of MAP, SkBF, and HR. An average relative value of the last 10-s of facial immersion was calculated for MAP and SkBF for comparison of total effect between conditions. However, an average relative value for each 5-s period during facial immersion was also calculated to show the time course of the response under each condition (3). The relative change from baseline was calculated for MAP and SkBF. For HR however, only absolute values were also calculated for each 5-s period during facial immersion as well as an average value during the last 10-s of immersion. All values represent the mean ± SEM for 6 subjects. A paired student t-test was used for statistical analysis with differences being considered significant at $P<0.05$.

RESULTS

The heart rate (HR) reached during the last 10-s of immersion was significantly different from baseline under all conditions ($P< 0.05$, Fig. 2 & 3). The average HR nadir measured during the last 10-s of immersion for LBNP (61 ± 1 bpm), and PEH (80 ± 2 bpm) was different than both LBPP (46 ± 2 bpm) and Control (47 ± 1 bpm) ($P<0.05$, Table 2). The onset of bradycardia occurred at different times during immersion. Control

HR became significantly different from baseline at 10-s followed by PEH and LBNP at 15-s and then LBPP at 20-s (Fig. 3).

Each of the three conditions applied caused significant changes in HR from baseline resting before immersion ($P<0.05$; Table 2). Thus, the application of LBPP caused a 15 (±1) bpm decrease in HR while LBNP and PEH caused a 9 (±1) bpm and a 13 (±2) bpm increase respectively. Exercise also caused a 0.54 (±0.11)°C ($P<0.05$) elevation in T_{es} from pre-exercise values that remained elevated during the time in which immersion was performed. MAP increased approximately 45-50% from baseline during immersion for all conditions ($P<0.05$, Fig. 2A, Table 1). Exercise was effective in inducing post-exercise hypotension with a mean MAP decrease of 4.9±0.6 mmHg when compared to pre-exercise resting baseline ($P<0.05$).

A marked reduction in SkBF was observed for all immersions at both the acral and non-acral sites ($P<0.05$; Fig. 2-B,C Table 1) however, there were no differences among conditions. The magnitude of the reduction in flow was much greater at the acral than the non-acral site with reductions of ~72% and ~33% respectively for all conditions ($P<0.05$; Fig. 2-B, C, Table 1).

DISCUSSION

This study was unique in examining the diving response during altered cardiac filling subsequent to modification by lower body pressure and exercise. The most important finding was that various conditions that reduce cardiac filling do attenuate diving bradycardia. The diving response was produced in each of the four conditions applied in this study, however the pattern and magnitude of the responses differed

significantly. These results support previous postulates that diving bradycardia may be attenuated due to reduced cardiac filling either as a result of exogenous heat stress (5) or as a result of high intrathoracic pressure (1).

During LBNP (7, 9) and PEH (29) efferent sympathetic activity is increased through a baroreflex arc to maintain peripheral vascular resistance while during LBPP (13), cardiac parasympathetic activity is increased. Both apnea and cold stimulation by the water promote chronotropic parasympathetic stimulation via the vagus nerve (2). Thus, performing apneic facial immersion during LBNP or PEH sets up two independent stimuli that give rise to conflicting inputs of a common effector at the level of the brain stem. Our results suggest that when sympathetic efferent activity to the heart is increased due to reduced cardiac filling, diving bradycardia is attenuated. As a result of increased efferent sympathetic activity, the diving induced parasympathetic response is either inhibited or attenuated, thus reducing the bradycardia observed. In addition to the previously mentioned influences on the diving response, it is important to note that feedback as a result of respiratory muscle inhibition and chemoreceptor stimulation are key components of the response (14). It was assumed that such influences were not altered by the experimental variables used in our protocol. Feedback subsequent to respiratory muscle inhibition and chemoreceptor stimulation was considered to be standardized in our study with each dive being limited to 30 seconds.

Facial immersion during PEH resulted in the greatest attenuation in diving bradycardia. During PEH not only is pre-load compromised as a result of blood pooling in the previously active musculature (15, 23, 24) but systemic hypotension exists (16, 17). It is reasonable to assume that the magnitude of the cardiac efferent sympathetic

activity generated during systemic hypotension (29) would be greater than that generated by cardiopulmonary baroreceptor unloading with no change in mean arterial pressure. It is possible that because of this greater magnitude of cardiac sympathetic outflow during PEH that diving bradycardia showed a greater attenuation than with LBNP.

While reducing cardiac filling resulted in an attenuation of bradycardia, increasing cardiac filling with LBPP did not amplify bradycardia beyond that of the Control condition. In order for the heart to maintain cardiac output at low heart rates, stroke volume must be increased. It is known that during diving bradycardia cardiac output falls because stroke volume cannot compensate totally to the reduction in HR. In the resting seated position with LBPP of +40mmHg used in this study, stroke volume is maximized (28); so regardless of increased cardiac filling, the magnitude of bradycardia may have been limited to maintain an adequate cardiac output. The use of LBPP in this study was thought to attenuate cardiac sympathetic activity, however, it is important to consider the possibility that in the population studied tonic sympathetic activity was low or negligible and thus LBPP had no effect on diving bradycardia.

It should be noted that our Control immersion produced the greatest effect on HR and this effect was consistent with other studies using the same immersion time and similar water temperature (5, 6). At the other extreme however, PEH exhibited the smallest bradycardic effect. However, the HR effects under the LBPP and LBNP conditions were also very different (Table 2). The average heart rate recorded in the last 10-s of immersion was very specific to each condition. As depicted in Fig. 3, heart rates stabilized at higher values when cardiac filling was compromised during LBNP (61 ± 1 bpm) and PEH (80 ± 2 bpm) as compared to the much lower rates achieved during LBPP

(46 ± 2 bpm) and Control (47 ± 1 bpm). This suggests that there is a mechanism that allows some of the diving–induced parasympathetic stimulation to act on the heart but there is a point at which sympathetic drive dominates control of HR. Any mechanism that modifies arterial blood pressure can, through the negative feedback loop of the baroreflex mechanism influence heart rate (7). Thus, the increased cardiac sympathetic activity during PEH (29) and LBNP (7) appear to dominate the afferent stimulus from facial immersion presumably through a baroreflex. Based on our results this influence is more pronounced during greater cardiovascular stress; that is PEH>LBNP>Control = LBPP.

In this study we also investigated the differences in cutaneous blood flow in acral (hand) and non-acral (forearm) regions during cutaneous vasoconstriction. In acral regions cutaneous arterioles are innervated only through noradrenergic sympathetic nerves and thus reflex changes, whether thermoregulatory or non-thermoregulatory are mediated by adjustments in vasoconstrictor tone (21). Non-acral skin however includes both a noradrenergic vasoconstrictor system (both α_1- and α_2-receptors) and a separate active vasodilator system still under investigation (11, 12, 32). While non-acral skin possesses two sympathetic neural pathways, the active vasodilator system is thought to play a prominent role during heat stress (21). To our knowledge the potential differences between these two regions of skin have not been examined during facial immersion. Our data showed a greater percentage reduction in acral blood flow (~72%) than non-acral (~33%) when comparing either absolute values or when values were normalized to maximal cutaneous vascular conductance (data not shown). The results show that peripheral vasoconstriction was produced in both skin regions but the reason for the greater percentage reduction in acral skin is not completely clear. Further investigation is

required to examine the differences between acral and non-acral regions. Specifically, it should be examined under conditions where blood flow levels during pre-dive baseline are nearly equal between regions.

When examining the results globally, the fact that the experimental conditions resulted in an altered heart rate response but did not affect reductions in SkBF or the rise in MAP is noteworthy. Arnold and Nadel (5, 6) suggested that peripheral vasoconstriction is a requirement for diving bradycardia and noted that there is relatively linear relationship between heart rate changes and changes to forearm blood flow. However, Finley et al. (10) previously concluded that the pharmacologic blockade of vasoconstriction and the increase in MAP did not affect the reflex diving bradycardia. Thus, the peripheral vasoconstriction and rise in MAP are not essential for diving bradycardia to occur but are merely coincidental (10). Our results show that despite the varying degrees of bradycardia as a result of the experimental conditions, the acute reduction in SkBF and rise in MAP were unaffected. This observation supports the idea that while both parasympathetic and sympathetic efferents are activated during facial immersion, the responses they effect are independent of each other.

The results show that reducing cardiac filling pressure and to a greater extent, inducing mild hypotension through exercise will attenuate the cardiac parasympathetic effects normally exhibited during facial immersion. The fact that peripheral blood flow and MAP changes were not different between conditions supports the idea that during facial immersion, cardiac and peripheral responses are exerted separately.

ACKNOWLEDGEMENT

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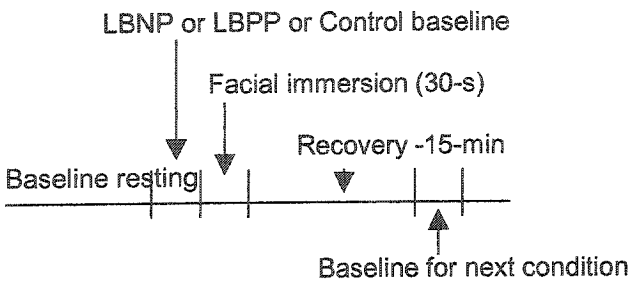
Session 1



Session 2

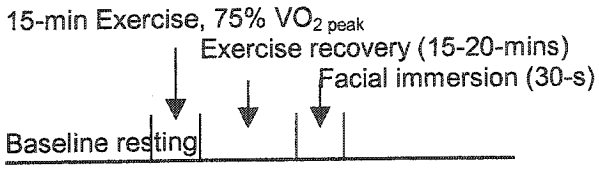


Fig. 1. Overview of protocol timeline for experimental session 1 - Control, LBNP, & LBPP immersion conditions and for experimental session 2 – Post-exercise hypotension immersion.

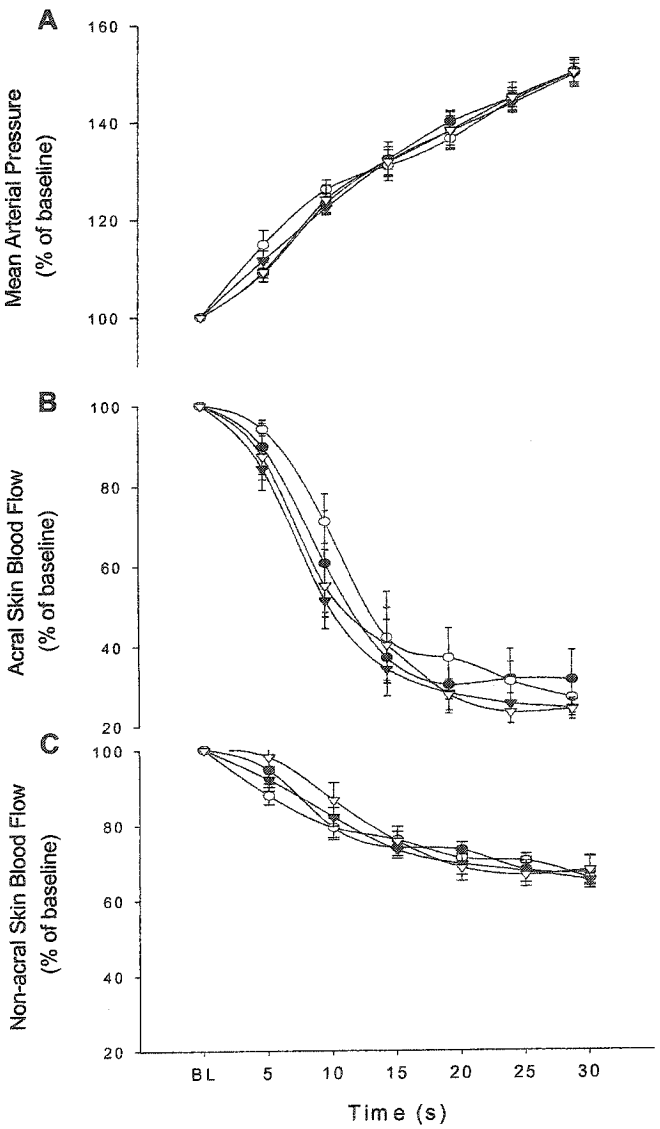


Fig. 2. Relative change from baseline for mean arterial pressure (A, *top*), acral skin blood flow (B, *middle*) and non-acral skin blood flow (C, *bottom*) for the Control (▽), PEH (▼), LBNP (○) and, LBPP (●) treatment conditions for each 5-s interval during the 30-s facial immersion. Values are means ± SEM for each 5-s interval, n = 6 subjects.

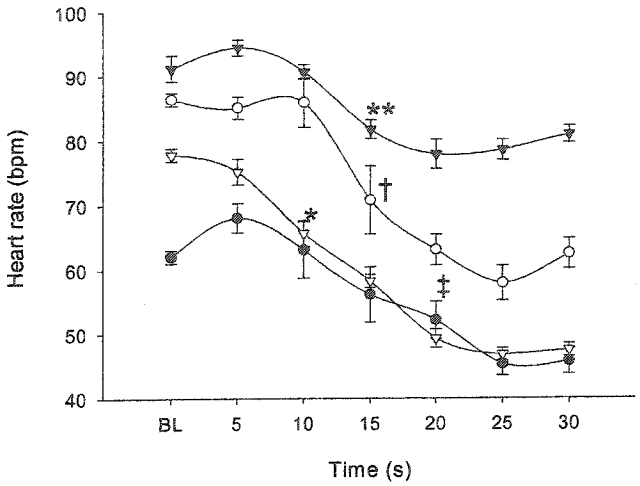


Fig. 3. Absolute heart rate responses during 30-s facial immersion for each 5-s interval for the Control (▽), PEH (▼), LBNP (○) and, LBPP (●) treatment conditions. Values represent the mean heart rate ± SEM for each 5-s interval for 6 subjects. Times in which values became significantly different ($P<0.05$) from baseline are denoted as follows: * Control, ** PEH, † LBNP, and ‡ LBPP.

Table 1. *Mean percentage change from pre-dive baseline to mean value measured during last 10-s of immersion.*

	Control	LBNP	LBPP	PEH
MAP	+47 (±3)	+47(±3)	+47 (±2)	+48 (±2)
SkBF				
acral	-77 (±3)	-71 (±5)	-69 (±8)	-74 (±3)
non-acral	-33 (±3)†	-32 (±4)†	-32 (±2)†	-34 (±3)†

Values are means ± SEM, n = 6 subjects. †, denotes significant difference from acral skin blood flow reduction ($P<0.05$)

Table 2. *Absolute heart rate values in beats per minute.*

	Control	LBNP	LBPP	PEH
Pre-condition	78 (±1)	77 (±1)	77 (±1)	78 (±2)
Baseline	---	86 (±1)*	62 (±1)*	91 (±2)*
Last 10-s	47 (±1)†	61 (±1)†	46 (±2)†	80 (±2)†

Baseline measurements represent the effect of the experimental condition on heart rate before immersion. Mean heart rates during the last 10-s of immersion are also shown. *, denotes significant difference from resting pre-condition heart rate ($P<0.05$). †, denotes significant difference from baseline ($P<0.05$).

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Hemodynamic and thermal responses to lower body positive and negative pressure during seated recovery from dynamic exercise.

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ABSTRACT

It was hypothesized that the application of lower body positive pressure (LBPP) and lower body negative pressure (LBNP) would modify the cardiovascular response associated with the postexercise period and that this may affect the skin blood flow (SkBF) response during thermal recovery. The purpose of this study was to investigate the hemodynamic and thermal responses to LBPP, LBNP and no pressure (control) recovery conditions in the upright seated posture. Six subjects were randomly exposed to 1) + 45 mmHg LBPP, 2) -20 mmHg LBNP or 3) no pressure (Control) for 45-mins after performing 15-mins of cycle ergometry exercise at 70% of their VO_{2peak} . Measurements included SkBF, mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), stroke volume (SV), total peripheral resistance (TPR), mean skin temperature (T_{Sk}), esophageal temperature (T_{es}). Exercise reduced MAP, SV, TPR at 15-mins postexercise significantly as compared to Baseline values in all conditions ($P < 0.05$). Conversely HR and T_{es} were significantly elevated at the same time when compared to baseline ($P < 0.05$). SkBF, T_{Sk} and CO remained unchanged from baseline. The application of LBPP caused a significant increase in SV, MAP, TPR and SkBF over 15-mins values between 15 and 60-mins of recovery ($P< 0.05$). HR was significantly reduced in the same time period ($P < 0.05$). LBNP resulted in SV, HR, SkBF and MAP remaining the same as post-exercise values throughout the recovery period. The control condition resulted in a time dependent recovery of baseline hemodynamics which achieved baseline values by 60-mins. LBPP appeared to accelerate the recovery of baseline hemodynamic values while LBNP maintained the postexercise hemodynamic status and the Control condition hemodynamics recovered in a time-dependent manner by 60-mins. We conclude that 1) lower extremity blood volume displacement using LBPP accelerates recovery of baseline hemodynamics while LBNP exacerbates the postexercise hemodynamic state relative to normal resting recovery; and 2) altering postexercise hemodynamics via LBPP may affect the thermoregulatory response of SkBF, presumably through a baroreceptor mediated mechanism.

Key words: LBPP, LBNP, postexercise, hemodynamics, skin blood flow

INTRODUCTION

The recovery period from dynamic exercise is associated significant cardiovascular and thermoregulatory adjustments (2, 22). Such changes are thought to be associated with post-exertional syncope and orthostatic intolerance (22). While both the hemodynamic and thermal changes have been characterized during exercise recovery the potential integrated effect of these responses has not been considered.

Dynamic exercise is associated with a prolonged elevation in esophageal temperature (T_{es}) (~0.3 °C) (15, 21). Paradoxically, skin blood flow (SkBF) and mean skin temperature (T_{sk}) return to baseline values despite the sustained elevation in T_{es} (35). As a result of reduced SkBF, there would be a time-dependent transfer of the residual heat of the muscle to the skin during the post-exercise resting period. Therefore, in the absence of a post-exercise increase in the heat-loss response (SkBF), T_{es} would remain elevated as long as: 1) the heat content of the muscle remains higher than that of the core, and/or 2) the PEH effect is removed (21).

Recovery from dynamic exercise in the seated position is frequently associated with postexercise hypotension (PEH). During PEH, mean arterial pressure (MAP) is reduced via both neural and vascular phenomena ((10-12). PEH is thought to occur in part as a result of venous pooling in the previously active musculature (3) and its magnitude also varies with the postexercise elevation in T_{es} (21). In the seated recovery position, removal of the muscle pump and the upright posture has transient deficits of return over output as blood accumulates in the venous capacitance system thus compromising cardiac pre-load (10, 22). Such an increase in venous pooling would reduce cardiac filling and unload baroreceptors (37).

Nonthermoregulatory baroreflex modulation of SkBF has been thoroughly described (16). A reasonable postulate is that the reduced SkBF (despite elevated body temperature) during exercise recovery may be due to baroreceptor unloading. Recent observations by Kenny et al. (20) and Jackson et al. (15) of a baroreceptor-mediated influence on post-exercise SkBF provides further evidence to suggest that post-exercise temperature regulation may be preceded by the need to regulate post-exercise blood pressure. Additional studies have demonstrated increases in forearm blood flow with the application of lower body positive pressure (LBPP) (33) while others have shown reductions in peripheral blood flow with the application of lower body negative pressure (LBNP) (4, 37). Thus, techniques that alter postexercise hemodynamics (LBPP, LBNP) may alter baroreceptor stimulation and conceivably the thermoregulatory response of SkBF. Application of mild LBNP reduces cardiac filling pressure through venous pooling (31, 36) and unloads cardiopulmonary baroreceptors (13, 14). Conversely, LBPP creates a greater venous pressure gradient that tends to increase cardiac filling and load cardiopulmonary baroreceptors (7).

To date, hemodynamic responses to LBNP (31) and LBPP (29) in the upright seated position have only been described at rest and during exercise. The cardiovascular responses to lower body pressure in the postexercise period remain uncharacterized. Thus, the purpose of this study was the examine the cardiovascular response to lower body pressure during seated recovery from 15-mins of dynamic exercise, and secondarily to examine thermoregulatory responses that may occur subsequent to the hemodynamic adjustments.

It was hypothesized that the application of lower body positive pressure (LBPP) and lower body negative pressure (LBNP) would modify the cardiovascular response associated with the postexercise period and that this may affect the skin blood flow (SkBF) response during thermal recovery.

METHODS

Subjects

Six healthy, physically active men volunteered and gave written consent to participate in this study. The study was approved by the Research Ethics Board of the University of Ottawa. Five to seven days before the experiments, peak oxygen consumption (VO_{2peak}) was measured during a progressive cycle ergometer protocol. The VO_{2peak} data were used to select the submaximal workload for the experimental exercise phase of the study. Subjects were (mean ± SE) 23 ± 1 years old, 174 ± 2 cm tall, weighed 77 ± 3 kg. Their mean VO_{2peak} was 43.4 ± 2.2 $ml \cdot kg^{-1} \cdot min^{-1}$.

Measurements

Heart rate (HR) was monitored using a Polar coded transmitter, recorded continuously and stored with a Polar Advantage interface and Polar Precision Performance software (Polar Electro Oy, Finland). Mean arterial pressure (MAP) was estimated from the integration of a non-invasive recording of blood pressure at the middle digit of the left hand (Finapres 2300, Ohmeda, Madison, WI, USA) fixed at heart level (the third intercostal space). The Finapres system is based on the volume clamp method (dynamic unloaded arterial wall principle) introduced by Penaz. MAP was verified periodically throughout the protocol by auscultation.

Pulmonary VO_2 was estimated with a metabolic cart (model CPX/D, Medgraphics, St. Paul, MN). Cardiac output (CO) was estimated using the CPX/D computerized version of the CO_2-rebreathing technique of Defares (5). It has been shown that Doppler-derived aortic blood flow (CO) measurements correlate well with the indirect carbon dioxide rebreathing method (9). The Defares method has also been shown to work well in "unsteady state" testing (27). Stroke volume (SV) was calculated as CO/HR. Total peripheral resistance (TPR) was calculated as MAP/CO.

Skin blood flow (SkBF) was estimated using laser-Doppler velocimetry (PeriFlux System 5000, Main control unit; PF5010 LDPM, Function unit; Perimed AB, Stockholm, Sweden) at the right mid-anterior forearm. The laser-Doppler flow probe (PR 401 Angled Probe, Perimed AB, Stockholm, Sweden) was taped to cleaned skin, in an area which did not appear by visual inspection overly vascular and from which consistent readings were noted (26). Because the focus of the study was on the recovery period, SkBF was not recorded during exercise.

Body temperature was recorded from several sites. Thus, central body temperature (esophageal temperature,T_{es}) was monitored continuously using a pediatric esophageal temperature probe (Mon-a-therm®, Mallinckrodt Medical, St-Louis, USA) inserted through the nares to a depth one-fourth of the standing height of the subject, whereby the tip of the thermocouple is estimated to be at the level of the left atrium (28). Skin temperature was recorded at 11 sites using heat flow sensors (Concept Engineering, Old Saybrook, CT, USA, model FR-025-TH44018-6). The area-weighted mean skin temperature ($\bar{T}_{sk}$) was estimated by calculating the weighted mean value whereby the following regional percentages were assigned: head 6%, upper arm 9%, forearm 6%,

finger 2%, chest 19%, upper back 9.5%, lower back 9.5%, anterior thigh 10%, posterior thigh 10%, anterior calf 9.5%, and posterior calf 9.5%. Temperature data were collected and digitized (Hewlett-Packard data acquisition module, model 3497A) at 30-s intervals, displayed graphically in real time and stored on hard disk (Hewlett-Packard, model PC-312, 9000).

The lower body negative pressure (LBNP) and lower body positive pressure (LBPP) conditions were created by inserting the subject up to the hips in a pressure chamber, sealed with a neoprene skirt at the level of the iliac crest. The chamber was designed to permit creating both hyperbaric and hypobaric conditions about the lower body segments with the subject in an upright semi-seated position.

Experimental protocol

Each subject performed a total of 3 experimental trials carried out in random order. Experiments were separated by a minimum of 48-hours during which subjects were instructed to avoid physical activity and excessive stressors such as exposure to hot or cold temperatures, particularly during the period between awakening and experimentation and during transit from home to the laboratory. Further, they were asked to fast at least 4 h prior to experimentation, and water ingestion was permitted during this time. Upon arrival to the laboratory, subjects were clothed in shorts and athletic shoes and were fitted with the appropriate instruments. All experimental trials were performed at an ambient temperature of 22.1 ± 0.6 °C. A schematic of the experimental timeline is presented in Figure 1.

After the subjects were instrumented, a 10-minute baseline recording was performed. Subjects then completed 15-mins of exercise on the cycle ergometer at 70%

of their VO_{2peak}. This intensity of exercise has been previously reported to elicit PEH (24, 25). Upon completion of exercise subjects were then transferred to the lower body pressure box and placed in the up-right semi-seated position. The time between completion of exercise and the commencement of one of the three pressure conditions was 15-minutes. Subjects were then exposed to either -20 mmHg LBNP, +45 mmHg LBPP or no lower body pressure (Control) for the remaining 45-minutes of the protocol. To avoid the potential confounding influence of circulating air on the lower extremities, the subjects donned light-weight spandex pants. In addition to controlling for circulating air between the LBPP and control conditions, air was circulated thru the box during the control condition with the seal of the chamber opened slightly to prevent the build up of pressure on the lower extremities.

Data Analysis

For all continuous measures a 2-minute average value was determined at each of the following time points: Baseline, End-Exercise, Pre-pressure (15-mins post-exercise), and at 30, 45, 60-mins postexercise (with pressure). CO, SV, HR, & TPR represent the average of two measures. All values represent the means ± SE for six subjects. A two-way ANOVA was used to compare the values with the two main factors of the ANOVA being time and pressure condition. When significant main effects were observed a Tukey's Post Hoc test was performed. Differences were considered significant when $P < 0.05$.

RESULTS

The mean values at each time point in the experiment for CO,SV,HR,MAP, TPR and SkBD in each of the three experimental conditions are displayed in Table 1. Differences related to the effect of time are also denoted in Table 1. The results depicting the effect of each condition during recovery from exercise are presented graphically in Figures 2- A,B,C and 3- A,B. Baseline values for all parameters, were not different between conditions. For each condition exercise caused a significant increase in CO, SV, HR and MAP and significant decrease in TPR ($P < 0.05$; Table 1). The exercise values achieved for each parameter were not different between conditions. Exercise resulted in significant changes in SV, HR, MAP, and TPR at 15-mins postexercise when compared with baseline ($P<0.05$; Table 1). CO values were unchanged. Specifically, SV, MAP, and TPR were significantly reduced from baseline while HR was elevated ($P < 0.05$; Table 1). These changes were similar across all conditions.

CO was not changed by any of the treatment conditions throughout recovery (Fig. 2-A). SV immediately increased significantly by 30-mins with the application of LBPP ($P < 0.05$; Table 1, Fig 2B). LBPP SV was 88 ± 5 mL and was significantly different from both LBNP and Control at 30-mins ($P < 0.05$; Table 1, Fig. 2B). LBPP SV had returned to the baseline value at 30-mins. LBPP SV continued to rise and remained significantly higher than both LBNP and Control throughout recovery ($P<0.05$; Table 1, Fig. 2B). Conversely LBNP remained at 15-mins values throughout recovery and was significantly lower than both LBNP & control at 45 & 60-mins ($P<0.05$; Table 1, Fig. 2B). Control SV gradually increased throughout recovery and was significantly lower and higher than LBPP and LBNP SV respectively ($P<0.05$; Table 1, Fig. 2B).

Heart rate. At 30-mins postexercise; that is after 15-mins of LBPP application, HR decreased significantly from 15-mins in the LBPP condition ($P < 0.05$; Table 1, Fig. 2C). LBPP HR was 72 ± 4 bpm and was significantly lower than LBNP and Control at 30-mins ($P < 0.05$; Table 1, Fig. 2C). HR remained significantly higher than baseline for LBPP at 30-mins ($P < 0.05$).

Mean arterial pressure. At 30-mins postexercise; that is after 15-mins of LBPP application, MAP remained increased significantly and remained higher than Control MAP only until 45-mins ($P<0.05$; Table 1, Fig. 3A). LBNP MAP was not different from Control or LBPP MAP throughout recovery.

Total peripheral resistance. At 30-mins postexercise; that is after 15-mins of LBPP application, TPR increased significantly in the LBPP condition and was significantly different from Control at 30 & 45-mins ($P < 0.05$, Table 1, Fig. 3B). LBNP TPR was not different from Control or LBPP TPR throughout recovery (Table 1, Fig. 3B).

SkBF. SkBF values were not different between conditions at any point in the protocol. In the LBPP condition SkBF increased significantly between 15-mins and 30mins ($P < 0.05$, Table 1.) and remained above 15-min and baseline values for the remainder of the protocol. In the Control and LBNP conditions SkBF remained unchanged from the 15-min values.

Temperature data

Mean values for T_{sk}, T_{es} and Heat Flux for each time point during the protocol are presented in Table 2. Exercise caused significant increases in T_{sk}, T_{es} and Heat Flux ($P < 0.05$) and the values were not different between conditions. At 30-mins T_{sk} in the LBPP

condition became significantly lower than the LBNP and control conditions. This coincided with significantly higher Heat Flux at the same time point ($P< 0.05$). Control T_{sk} remained higher than both the LBPP and LBNP conditions at 45-mins and 60-mins.

DISCUSSION

The data from this study supports the idea that lower body positive and negative pressure application alters the cardiovascular responses associated with recovery from dynamic exercise. We observed that these changes occur in a time dependent manner and that the nature of the changes were unique to the experimental condition. Furthermore, despite no change in CO between conditions, the restoration of SV and MAP by application of LBPP was concurrent with increases in SkBF. This response was not observed in the LBNP and Control conditions. Such observations are consistent with previous studies demonstrating a baroreceptor-mediated influence on peripheral blood flow at rest and during exercise (4, 16), and altered regulation of skin blood flow during recovery from exercise (15, 20). Also of note in this study is that the hemodynamic responses to the application of lower body pressure during recovery from exercise were not consistent with responses observed when lower body pressure was applied at rest in other studies (29, 31).

The observation that application of lower body pressure did not significantly alter CO but did change SV and HR is important to note. We speculate that this is due to altered hemodymanics during the postexercise period. In the seated recovery position, the absence of the muscle pump and having an upright posture favors venous pooling thus compromising cardiac pre-load (10, 22). In addition, postexercise hypotension may exist

thus reducing afterload. Despite a reduced preload, increased ionotropy of the heart, elevated heart rate and reduced afterload serve to maintain or even increase CO above pre-exercise values (22, 23). Our CO results at 15-mins postexercise were not significantly different from baseline values, however a significant reduction in SV and an increase in HR were evident.

Effect of LBPP. Application of LBPP creates a greater venous pressure gradient that tends to increase cardiac filling, central venous pressure and MAP (7, 34). In the upright posture higher hydrostatic pressure causes a pooling of ~600mL of blood in the lower part of the body (8). Thus the upright recovery posture would tend to exacerberate venous and muscle blood pooling associated with exercise recovery. By reversing venous pooling with LBPP we observed an increase SV, MAP, TPR and a reduction in HR. Such a response is typical of a baroreflex mediated bradycardia. It has been shown that resistance vessels in skeletal muscle remain dilated after a bout of dynamic exercise and the resultant hyperemia persists well into recovery (30, 32). It is possible that we did not see increases in SV comparable with normal resting because the combined effect of persistent muscle dilation and the upright posture may result in time dependent transfer of blood from the previously active muscle to the heart. The increased SV observed in our study during LBPP suggests that LBPP caused a marked translocation of blood from the lower to upper part of the body (29). Interestingly SV continued to increase throughout recovery despite increased afterload. However, MAP was not increased above baseline levels and some have suggested a greater ionotropic response during recovery (22, 23) which may have compensated for any increases in afterload. That fact that we did not observe an increase in CO with LBPP, suggests that either 1) there may not have been

enough available blood volume (if pooled in muscle) to promote further increases in SV sufficient to raise CO, or 2) despite an increased SV the baroreflex suppression of HR also prevented an increase in CO.

MAP was restored with the application of LBPP but the fact that CO was not elevated, suggests that MAP was the major determinant causing increased TPR. However, the mechanism underlying the increase MAP is unknown. A study by Nishiyasu et al. (29) ruled out the possibility of a mechanoreflex causing the increase in MAP because of different MAP responses between postures despite the same level of LBPP application. They did suggest however, that MAP may have been increased through the direct effect of LBPP on vascular conductance, and that the effect is more pronounced in the supine than upright posture.

Effect of LBNP. Application of mild LBNP reduces cardiac filling pressure through venous pooling (31, 36) and unloads cardiopulmonary baroreceptors (13, 14). LBNP is also characterized by a reduced central venous pressure that will tend to reduce stroke volume and arterial pressure (1, 17). We did not observe a reduction in SV or MAP with the application of LBNP in the upright posture. During recovery from exercise SV was already reduced significantly from baseline which means the capacity to observe a reduction in SV with LBNP may have been diminished when compared to normal resting SV values. However, SV remained at pre-LBNP levels (15-mins) throughout the application of LBNP while MAP increased slightly such that hypotension did not exist relative to baseline MAP. While the maintenance of reduced SV was expected due to prolonged venous and muscle blood pooling, the fact that MAP became no different from baseline was not anticipated. A study by Tripathi et al. (37) concluded that reduced

cardiac filling pressure during LBNP appears to act via low-pressure baroreceptors and initiates compensatory cardiovascular reflexes to increase venous tone. Thus, it is possible that LBNP of –20 mmHg used in this study was sufficient to elicit reflex peripheral vasoconstriction which would tend to defend MAP. Also of note in our LBNP data is the absence of a reflex increase in HR upon application of pressure. A previous investigation in our lab using –20 mmHg in the upright posture at rest, demonstrated a significant reflex increase in HR of about 9 ± 1 bpm (18). Others have also reported reflex increases in HR in both the upright (31) and the supine postures (6, 36, 37). While there was not a reflex increase in HR upon LBNP application, the postexercise HR (which was elevated ~ 25 bpm above baseline) remained elevated for the duration of the protocol. This was contrary to the Control condition which showed a gradual reduction in HR during the throughout recovery. While it is only speculative, we suspect our observations may be consistent with changes in baroreflex function and autonomic control of HR after exercise. Further investigations should examine this response during recovery from exercise.

Effect of Control. Our results were typical of an exercise recovery response in the upright posture. We observed an elevated HR that gradually decreased towards baseline over the 60-mins recovery period. In addition there was a time dependent increase in SV, MAP and TPR towards baseline. Theses trends are consistent with others who have examined exercise recovery hemodynamics (2, 21, 22). When comparing the results of the Control condition with that of LBNP and LBPP, it appears that without facilitating the removal of blood from the lower extremities and previously active muscles, there is a time dependent recovery of baseline hemodynamics. Our results suggest that reversal of

venous and muscle blood pooling via LBPP accelerates this process while compromising this process with LBNP exacerbates the postexercise hemodynamic state. Such an observation suggests that recovery mode and posture may be important in maintaining blood pressure and potentially avoiding syncopal episodes that commonly occur at the cessation of exercise (19).

Thermoregulatory responses. Exercise resulted in an elevation in body temperature as represented by esophageal temperature of approximately ~0.3 °C when measured at 15-mins postexercise. Despite this persisting perturbation in the thermoregulatory system, SkBF had returned to baseline levels 15-mins postexercise. We are proposing that this paradoxical response of reduced SkBF with elevated body temperature is a consequence of postexercise hemodynamics. Specifically, increased venous and muscle blood pooling in addition to postexercise hypotension results in reduced central blood volume and cardiac pre-load which tend to unload baroreceptors. It has previously been demonstrated that peripheral blood flow is subject to non-thermal baroreflex modulation (4, 16, 33, 37). Recent observations by Kenny et al. (20) and Jackson et al. (15) of a baroreceptor-mediated influence on post-exercise SkBF provides further evidence to suggest that post-exercise temperature regulation may be preceded by the need to regulate post-exercise blood pressure. However, these studies did not have hemodynamic measures to probe possible changes in CO and SV in the recovery period. Our results suggest that restoring cardiac pre-load and MAP with LBPP (which would tend to increase stimulation of baroreceptors), augments SkBF. While use of laser-Doppler velocimetry to examine SkBF responses can be site dependent, the LBPP condition was the only condition to show significant increases in SkBF between 15-60-

mins of recovery. Conversely, the maintenance of venous and muscle blood pooling with LBNP resulted in no change in SkBF during the recovery period. Our observations of increased SkBF with the application of LBPP during recovery from exercise support the idea that altered hemodynamics during inactive recovery from exercise may compromise postexercise temperature regulation. Specifically, it appears as though afferent and efferent feedback associated with blood pressure control appear to override the thermoregulatory response of SkBF that is often associated with elevated body temperature. However it is important to note that the increases in SkBF observed in this experiment may not have been due to elevated body temperature, but only due to the reflex associated with LBPP application.

We conclude that 1) lower extremity blood volume displacement using LBPP accelerates recovery of baseline hemodynamics while LBNP exacerbates the postexercise hemodynamic state relative to normal resting recovery; and 2) altering postexercise hemodynamics via LBPP may affect the thermoregulatory response of SkBF, presumably through a baroreceptor mediated mechanism. Further investigations should examine the role of the cardiovascular system in modulating heat transfer and exchange during recovery from exercise.

ACKNOWLEDGEMENT

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Figure 1.

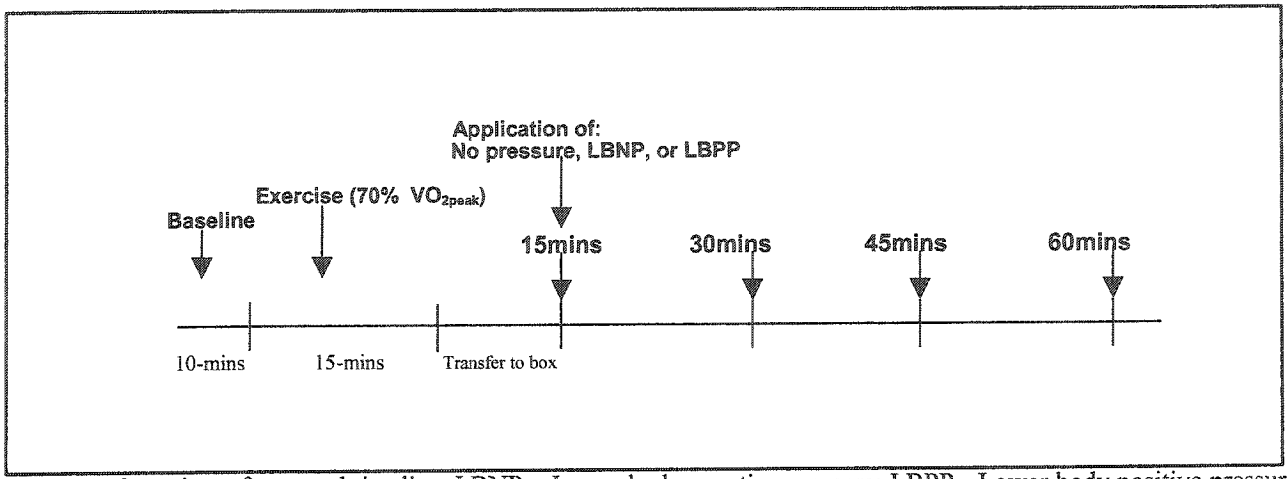

Figure 1. Overview of protocol timeline. LBNP – Lower body negative pressure; LBPP - Lower body positive pressure; VO_{2peak} -- peak oxygen consumption

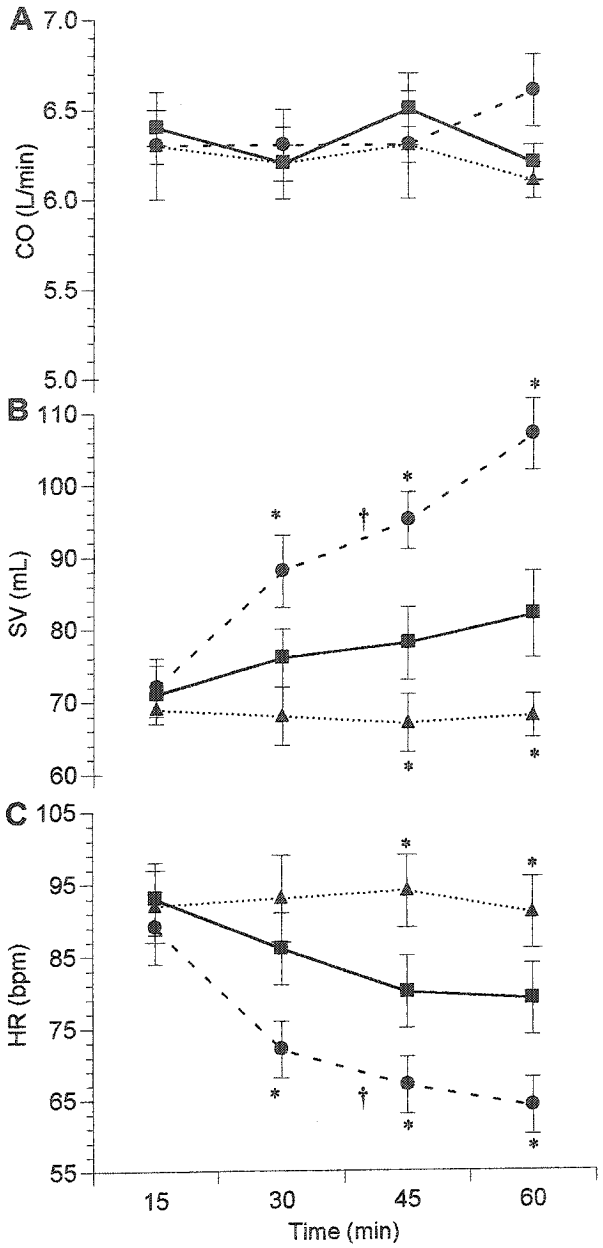

Figure 2. Cardiac output (CO), stroke volume (SV) and heart rate (HR) for lower body negative pressure (LBNP) (▼), for lower body positive pressure (●) (LBPP), and Control (■). Pressure application occurred after 15-mins. Values represent means ±SE for 6 subjects. * Denotes significant difference from Control. † denotes significant difference between LBPP and LBNP at 30-mins.

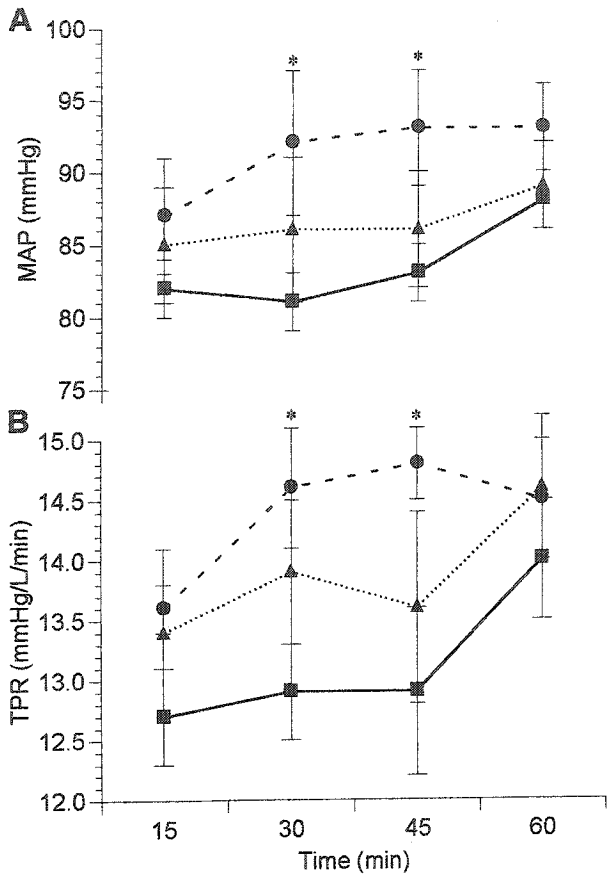

Figure 3. Mean arterial pressure (MAP), total peripheral resistance (TPR) and for lower body negative pressure (LBNP) (▼), for lower body positive pressure (●) (LBPP), and Control (■). Pressure application occurred after 15-mins. Values represent means ±SE for 6 subjects. * denotes significant difference from Control condition ($P<0.05$).

Table 1. Mean hemodynamic values for CO, SV, HR, MAP & TPR, SkBF

					Pressure period		
		Baseline	Exercise	15-mins (Pre-presure)	30-mins	45-mins	60-mins
CO (L/min)			#	##			
	Control	6.1± 0.1	21.5 ± 1.1	6.4 ± 0.1	6.2 ± 0.1	6.5 ± 0.2	6.2 ± 0.1
	LBPP	5.8 ± 0.2	21.8 ±1.1	6.3± 0.1	6.3 ± 0.2	6.3 ± 0.1	6.6 ± 0.2
	LBNP	6.1 ± 0.2	21.5 ± 1.0	6.3 ± 0.3	6.2 ± 0.1	6.3 ± 0.3	6.1 ± 0.1
SV (ml/min)			#	##		††	††
	Control	91 ± 7	127 ± 6	71 ± 4	76 ± 4	78 ± 5	82 ± 6 ‡
	LBPP	88 ± 4	131 ± 7	72 ± 4	88 ± 5 * ‡	95 ± 4 ‡	107 ± 5 ‡
	LBNP	92 ± 4	128 ± 6	69 ± 2	68 ± 4	67 ± 4	68 ± 3
HR (bpm)			#	##		††	††
	Control	69 ± 5	169 ± 5	93 ± 5	86 ± 5	80 ± 5 ‡	79 ± 5 ‡
	LBPP	65 ± 3	166 ± 6	89 ± 5	72 ± 4 * ‡	67 ± 4 ‡	64 ± 4 ‡
	LBNP	67 ± 4	168 ± 5	92 ± 5	93 ± 6	94 ± 5	91 ± 5
MAP (mmHg)			#	##			
	Control	92 ± 3	112 ± 3	82 ± 3	81 ± 3	83 ± 3	88 ± 3 ‡
	LBPP	95 ± 3	111 ± 3	87 ± 2	92 ± 2 † ‡	93 ± 2 † ‡	93 ± 2 ‡
	LBNP	93 ± 3	111 ± 3	85 ± 4	86 ± 5	86 ± 4	89 ± 3
TPR (mmHg/L*min^{-1})			#	##			
	Control	15.1 ± 0.6	5.2 ± 0.3	12.7 ± 0.4	12.9 ± 0.4	12.9 ± 0.7	14.0 ± 0.5‡
	LBPP	15.9 ± 0.4	5.2 ± 0.3	13.6 ± 0.2	14.6 ± 0.5 †‡	14.8 ± 0.3† ‡	14.5 ± 0.5 ‡
	LBNP	15.2 ± 1.0	5.3 ± 0.2	13.4 ± 0.7	13.9 ± 0.6	13.6 ± 0.8	14.6 ± 0.6

Table 1. Values are means ± SE for 6 subjects. CO, Cardiac output; SV, Stroke volume, HR, Heart rate; MAP, Mean arterial pressure; TPR, Total peripheral resistance.
(#) All values in column are significantly different from Baseline and 15-mins. (##) All values in column are significantly different from Baseline and exercise. (*) Significant difference from two other conditions only. (†) Significantly different from control only. (††) All conditions are significantly different from each other. (‡) Significantly different from 15-mins. Differences considered significant at $P < 0.05$.

Table 1 continued...

SkBF (PU)							
	Control	11.0 ± 0.5	N/a	11.2 ± 0.8	11.1 ± 0.7	12.8 ± 1.0	13.4 ± 1.4
	LBPP	10.3 ± 0.2	N/a	9.2 ± 0.7	12.7 ± 1.2 ‡	15.1 ± 1.8 ‡	15.8 ± 1.7 ‡
	LBNP	11.0 ± 2.2	N/a	12.7 ± 2.8	13.0 ± 2.4	11.4 ± 2.8	11.4 ± 1.9

Same legend as previous page applies to the above table.

Table 2. Mean values for Tes, Tsk & Flux

					Pressure		
Tes		Baseline	Exercise	15-mins	30-mins	45-mins	60-mins
	Control	36.98 ± 0.15	37.81 ± 0.32 †	37.27 ±0.20	37.12 ± 0.20	37.00 ± 0.19	36.96 ± 0.16
	LBPP	36.97 ± 0.13	37.85 ± 0.18 †	37.26 ± 0.11	37.20 ± 0.12	36.99 ± 0.10	36.81 ± 0.09
	LBNP	36.92 ± 0.12	37.99 ± 0.21 †	37.29 ± 0.23	37.22 ± 0.21	37.14 ± 0.21	37.03 ± 0.16
Tsk							
	Control	33.75 ± 0.16	34.92 ± 0.12 †	34.71 ± 0.08	34.72 ± 0.08	34.75 ±0.08*	34.74 ±0.11*
	LBPP	33.64 ± 0.14	34.78 ± 0.18 †	34.54 ± 0.09	33.88 ±0.06*	34.15 ± 0.10	34.31 ± 0.15
	LBNP	34.09 ± 0.19*	35.20 ± 0.23 †	34.79 ± 0.22	34.49 ± 0.08	34.36 ± 0.10	34.26 ± 0.11
Flux							
(W/m^2)	**Control**	70.30 ± 2.47	119.25 ± 3.98†	65.17 ± 2.33	61.13 ± 2.00	58.14 ± 1.14	52.65 ± 2.09
	LBPP	68.05 ± 2.97	119.76 ± 4.62†	66.43 ± 1.02	80.71 ±1.97*	65.87 ± 3.14	60.42 ± 3.11
	LBNP	69.83 ± 2.10	118.48 ± 4.44†	64.68 ± 3.17	63.89 ± 2.98	58.28 ± 1.86	55.67 ± 2.21

Table 2. Values are means ± SE for 6 subjects. Tes, Esophageal temperature; Tsk, mean skin temperature; Flux, mean flux. (*) Significantly different from other two conditions only. (†) Exercise value is significantly different from baseline. Differences considered significant at $P < 0.05$.

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PART THREE:

DISCUSSION AND CONCLUSION OF THE ARTICLES

6.0 DISCUSSION

Blood pressure regulation in the human is of critical importance to whole body physiology. Arterial pressure is regulated by feedback control systems, operating in both the short and the long term, which rely on autonomic nerves and circulating hormones as their effector mechanisms (Dampney et al, 2002). Due to the fact that blood pressure is largely regulated by the autonomic nervous system, it may be subject to many conflicting influences at central signal integration sites in the brain. Such conflicting influences may be feedback subsequent to factors that may perturb blood pressure regulation. Such factors include posture, exercise and temperature. The overall focus of this thesis was to provide insight in to competing reflexes associated with cardiovascular and thermal control.

The first article examined cardiovascular control by observing the responses to the strong cardiac parasympathetic stimulus of cold water facial immersion under conditions of altered cardiac filling. The results suggest that the maintaining sufficient cardiac output appears to override the facial immersion stimulus provided in this study. Based on previous research it is known that the human diving response (as produced by facial immersion) is brain stem mediated such that both apnea and facial trigeminal nerve afferents contribute to the characteristic vagally mediated bradycardia (Arnold & Nadel, 1993; Andersson et al, 2000). However, it is also well known that the baroreflex arc results in changes in vagal tone via the nucleus tractus solitarius (Dampney et al 2002). Thus, while our conclusions are based on the known "controls" of heart rate and baroreflex function, only nerve recordings at the level of the heart or brain stem would reveal the true nature of the conflicting stimuli. Overall, it appears as though factors that would trigger reflexes to defend arterial pressure (LBNP and postexercise hypotension) appear to override what is thought to be a natural innate response to cold water facial immersion.

Conversely, augmenting cardiac filling with LBPP did not amplify the response beyond that of control suggesting that the while the facial immersion reflex is a coordinated pattern of events, it still respects the need to maintain arterial pressure. It should be noted that had we compromised cardiac filling to a lesser degree (Ie: less LBNP or milder exercise), perhaps the diving response may have fully developed. Had this been tested it would suggest that the magnitude of the competing stimuli would determine the observed hierarchy of control.

The second study in this set of work sought to better understand the interrelationship of postexercise hemodynamic and thermal responses. As described in the introduction, recovery from exercise is associated with two conflicting stimuli. They include 1) the persisting elevation in body temperature which should tend to increase SkBF and 2) the need to maintain arterial pressure in the face of reduced preload, venous and muscle blood pooling and significant hypotension. The common thread between these stimuli is the non-thermoregulatory baroreceptor modulation of both blood pressure and skin blood flow. Previous work has demonstrated baroreceptor modulation of peripheral blood flow at rest (Crandall et al 1996, Johnson, 1986) and more recently has been shown to influence vasomotor control during recovery from exercise (Jackson et al, 2003; Kenny et al, 2000). Once again it might be of no coincidence that all controls are integrated centrally. During heat stress the hypothalamus can effect a response via the nucleus tractus solitarius to reduce the tone on cutaneous blood vessels and or initiate active vasodilation. This response would be expected during recovery from exercise with the existence of mild hyperthermia, however postexercise hypotension and a reduction in pre-load serve to unload baroreceptors and initiate reflexes that defend blood pressure such as peripheral vasoconstriction. This postulate is reasonable as it has been well established that skin blood flow is on the efferent arm of the baroreceptor reflex. As noted above,

the baroreflex also synapses at the brain stem's nucleus tractus solitarius and thus serves as a site of conflicting thermal (hypothalamic) and cardiovascular (baroreceptor) inputs. While neither brain stem nerve recordings nor measures of sympathetic activity were obtained in this study, it is likely that baroreceptor loading via LBPP (Fu et al, 1999) would have a suppressive effect on sympathetic outflow to the heart (as demonstrated by the observed bradycardia) and blood vessels (as observed by the increased skin blood flow). Conversely, baroreceptor unloading via LBNP (Hisdal et al, 2001, 2002), likely maintained (via the baroreflex arc) sympathetic outflow / vagal withdrawl on the heart (as demonstrated by the prolonged elevated heart rate) and blood vessels (as demonstrated by the prolonged reduction in skin blood flow). Such conclusions are based on known responses to LBPP and LBNP, but it is possible that additional factors such as mechanoreceptors, metaboreceptors and thermal afferents may have also provided conflicting stimuli centrally and contributed to the observed response. The precise nature of these mechanisms is not however completely established in the current literature.

7.0 CONCLUSIONS & RECOMMENDATIONS

An overall conclusion of this work is that reflexes associated thermal stress may be compromised by the autonomic nervous system's drive to maintain arterial pressure. Specifically, the bradycardia associated with facial immersion (which some believe is an oxygen conserving effect) can be overridden when cardiac filling is compromised. Additionally, the augmentation of central blood volume (via LBPP) during exercise recovery appears to promote the thermoregulatory response of skin blood flow (presumably through a baroreceptor mediated mechanism).

While, the focus of the facial immersion experiment became the heart rate response, further investigations should look at the whole body response such that the volume redistribution associated with LBPP, LBNP and postexercise hypotension before facial immersion is better characterized. To do so, cardiac output, stroke volume, venous pooling and even changes in splanchnic and hepatic circulations should be quantified. Secondly, the "diving reflex" is considered by some to be a chemoreflex in humans because of the associated apnea. Thus, factors such as pCO_2 , pO_2 and cerebral blood flow should be examined in conjunction with the cardiovascular dynamics.

Relatively little literature exists examining the integrated thermal and cardiovascular response during exercise recovery as compared to rest and exercise. Future studies should further probe the relationship between postexercise hemodynamics and heat loss responses such that blood volume distribution, muscle blood flow and heat transfer and exchange kinetics are better characterized. Secondly, the differences in these actions should be compared between active and inactive recovery modes as well as between genders.

PART FOUR:

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APPENDIX 1:

Published version of Article #1 in Journal of Applied Physiology

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Cardiovascular responses to apneic facial immersion during altered cardiac filling

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Journeay, W. Shane, Francis D. Reardon, and Glen P. Kenny. Cardiovascular responses to apneic facial immersion during altered cardiac filling. *J Appl Physiol* 94: 2249–2254, 2003. First published February 21, 2003; 10.1152/japplphysiol.01140.2002.—The hypothesis that reduced cardiac filling, as a result of lower body negative pressure (LBNP) and postexercise hypotension (PEH), would attenuate the reflex changes to heart rate (HR), skin blood flow (SkBF), and mean arterial pressure (MAP) normally induced by facial immersion was tested. The purpose of this study was to investigate the cardiovascular control mechanisms associated with apneic facial immersion during different cardiovascular challenges. Six subjects randomly performed 30-s apneic facial immersions in 6.0 ± 1.2°C water under the following conditions: *1*) −20 mmHg LBNP, *2*) +40 mmHg lower body positive pressure (LBPP), *3*) during a period of PEH, and *4*) normal resting (control). Measurements included SkBF at one acral (distal phalanx of the thumb) and one nonacral region of skin (ventral forearm), HR, and MAP. Facial immersion reduced HR and SkBF at both sites and increased MAP under all conditions ($P < 0.05$). Reduced cardiac filling during LBNP and PEH significantly attenuated the absolute HR nadir observed during the control immersion ($P < 0.05$). The LBPP condition did not result in a lower HR nadir than control but did result in a nadir significantly lower than that of the LBNP and PEH conditions ($P < 0.05$). No differences were observed in either SkBF or MAP between conditions; however, the magnitude of SkBF reduction was greater at the acral site than at the nonacral site for all conditions ($P < 0.05$). These results suggest that the cardiac parasympathetic response during facial immersion can be attenuated when cardiac filling is compromised.

diving response; skin blood flow; lower body pressure; blood pressure

THE HUMAN DIVING RESPONSE is initiated by apnea and is augmented by facial immersion in cold water (14). This reflex response is characterized by a reduction in heart rate (HR) through vagus nerve action and by α-adrenergic vasoconstriction in selected vascular beds (2, 6, 14). Superficial cold receptors that are innervated by the ophthalmic branch of the trigeminal nerve enhance the cardiovagal activity involved in the response (18, 22, 31).

Although the mechanism of diving bradycardia is known to be parasympathetically mediated, it is unclear at this time how the response is changed during altered cardiac filling. Only a few studies have implicated reduced cardiac filling in the attenuation of bradycardia. Arnold and Nadel (5) demonstrated that diving bradycardia can be attenuated subsequent to an increased thermal load induced by exogenous heating in 68°C ambient heat. They contended that the attenuation of diving bradycardia occurs as a result of reduced cardiac filling due to peripheral redistribution of blood volume. It has also been demonstrated that high intrathoracic pressure may play a role in the degree of bradycardia observed. Andersson et al. (1) observed that the bradycardic effect was attenuated during periods of high intrathoracic pressure created at 85–100% of prone vital capacity. They concluded that high intrathoracic pressure occluded venous return impeding cardiac filling and thus attenuated the development of diving bradycardia. Although it has been suggested that adequate cardiac filling is a requirement for the development of the diving response, it has yet to be demonstrated directly. Because there appears to be a relationship between cardiac filling and the magnitude of diving bradycardia observed, manipulating factors that alter cardiac filling [postexercise hypotension (PEH), lower body pressure (LBNP)] may alter the bradycardic response.

Cardiac filling can be altered via different techniques. Application of mild LBNP reduces cardiac filling pressure through venous pooling (30, 33), unloads cardiopulmonary baroreceptors (19, 20), and increases efferent sympathetic activity (7). During PEH, mean arterial pressure (MAP) is reduced via both neural and vascular phenomena (15–17). PEH is thought to occur as result of venous blood pooling in the previously active musculature, and its magnitude varies directly with the postexercise elevation in esophageal temperature (T_{es}) (8, 23). In the PEH period, removal of the muscle pump and the seated posture has transient deficits of return over output as blood accumulates in the venous capacitance system, thus compromising preload (15, 24). In contrast, lower body positive pressure (LBPP) creates a greater venous pressure gradi-

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ent that tends to increase cardiac filling, load cardiopulmonary baroreceptors, and inhibit efferent sympathetic activity (13).

Thus the purpose of this study was to investigate the influence of cardiac filling on the diving reflex. Specifically, the study was undertaken to examine the interaction of the parasympathetic response arising from facial immersion and the simultaneous challenge created by the three experimental conditions of modified cardiac filling. It was hypothesized that reduced cardiac filling as a result of LBNP and PEH would attenuate the reflex changes to HR, skin blood flow (SkBF), and MAP normally induced by facial immersion.

METHODS

Subjects

Six healthy, physically active men volunteered and gave written consent to participate in this study. The study was approved by the Research Ethics Board of the University of Ottawa. Five to seven days before the experiments, maximal oxygen consumption ($\dot{V}O_{2\,max}$) was measured during a progressive treadmill protocol. The $\dot{V}O_{2\,max}$ data were used to select the submaximal workload for the experimental exercise phase of the study. Subjects were 23 ± 1 (SE) yr old, 176 ± 2 cm tall, and weighed 71 ± 2 kg. Their mean maximal aerobic capacity was 58.0 ± 2.3 $ml \cdot kg^{-1} \cdot min^{-1}$.

Measurements

HR was recorded continuously from precordial lead V on a Quinton 4000B electrocardiogram (Quinton Instruments, Seattle, WA). MAP was estimated from the integration of a noninvasive recording of blood pressure at the middle digit of the left hand (Finapres 2300, Ohmeda, Madison, WI) fixed at heart level (the third intercostal space). The Finapres system is based on the volume clamp method (dynamic unloaded arterial wall principle) introduced by Penaz. This method has proven to provide accurate measures of MAP in other studies examining facial immersion (1–3). These blood pressure data were recorded and stored continuously at 5-s intervals.

SkBF was estimated by using laser-Doppler velocimetry (PeriFlux System 5000, main control unit; PF5010 LDPM, function unit; Perimed, Stockholm, Sweden) at the left mid-anterior forearm and at the level of the distal phalanx of the thumb. The laser-Doppler flow probes (PR 401 Angled Probe, Perimed) were taped to cleaned skin, in an area which did not appear by visual inspection to be overly vascular and from which consistent readings were noted (26).

During the exercise component of the study, body temperature was recorded from several sites. Thus central body temperature (T_{es}) was monitored continuously by using a pediatric esophageal temperature probe (Mon-a-therm, Mallinckrodt Medical, St. Louis, MO) inserted through the nares to a depth one-fourth of the standing height of the subject, whereby the tip of the thermocouple is estimated to be at the level of the left atrium (27). Skin temperature was recorded at 11 sites by using heat flow sensors (model FR-025-TH44018-6, Concept Engineering, Old Saybrook, CT). The area-weighted mean skin temperature (T_{sk}) was estimated by calculating the weighted mean value, whereby the following regional percentages were assigned: head 6%, upper arm 9%, forearm 6%, finger 2%, chest 19%, upper back 9.5%, lower back 9.5%, anterior thigh 10%, posterior thigh 10%, anterior calf 9.5%, and posterior calf 9.5%. Temperature data were collected and digitized (model 3497A data acquisition module, Hewlett-Packard) at 5-s intervals, displayed graphically in real time, and stored on hard disk (model PC-312, 9000, Hewlett-Packard).

The LBNP and LBPP conditions were created by inserting the subject up to the hips in a pressure chamber, sealed with a neoprene skirt at the level of the iliac crest. The chamber was designed to permit creation of both hyperbaric and hypobaric conditions about the lower body segments with the subject in an upright semiseated position.

Experimental Protocol

Each subject performed a total of four experimental trials carried out in random order. The first experiment was conducted after a 36-h period during which subjects were instructed to avoid physical activity and excessive stressors such as exposure to hot or cold temperatures, particularly during the period between awakening and experimentation and during transit from home to the laboratory. Furthermore, they were asked to fast at least 4 h before experimentation, and water ingestion was permitted during this time.

Subjects were required to come to the laboratory for two experimental sessions at an interval of not less than 48 h. During the first experimental session, the subjects performed facial immersion under the LBNP, LBPP, and control conditions in random order. Arnold et al. (4) had their subjects perform multiple vagal maneuvers on the same day and allowed a minimum 3-min recovery interval between maneuvers. Thus we believe that performing multiple immersions with the recovery interval described below caused possible residual effects between conditions to be avoided. To avoid the residual effects of exercise, the exercise trial was performed on a separate day. The order in which *sessions 1* and *2* were carried out was also randomized. All trials were performed at an ambient temperature of 26°C. A schematic representation of the experimental timeline is presented in Fig. 1.

Session 1. Each condition began with a 5-min upright rest period during which baseline readings were taken (precondition baseline resting). The baseline resting period was carried out while the subject was in the pressure chamber to

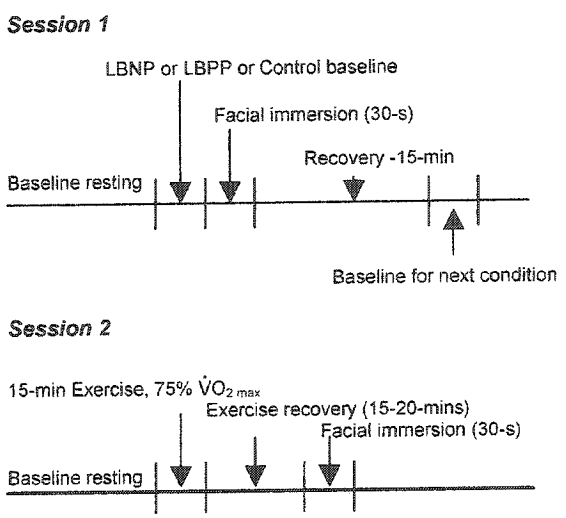

Fig. 1. Overview of protocol timeline for experimental *session 1* [control, lower body negative pressure (LBNP), lower body positive pressure (LBPP) immersion conditions] and for experimental *session 2* [postexercise hypotension (PEH) immersion]. $\dot{V}O_{2\,max}$, maximal oxygen consumption.

minimize the effect of posture across and within subjects for all measures. Subjects were then exposed to either −20 mmHg LBNP, +40 mmHg LBPP, or no lower body pressure (control). Once the subject was positioned within the pressure chamber and all cardiovascular parameters had stabilized, a 30-s baseline reading was recorded. Stabilization occurred in <5 min for all subjects. After baseline values had been registered under each condition, subjects then performed a 30-s apneic facial immersion in cold water (6.0 ± 1.2°C). The immersion time was predetermined and has been used by other studies (3, 5, 6). The water-filled container was placed below the subject's chin such that total facial immersion including the forehead and chin was achieved by simple flexion of the neck. Facial immersions were performed during a midinspiratory breath hold, and subjects were cautioned to avoid the Valsalva maneuver (5, 6). Recordings were continued for 2 min postimmersion, and there was a 15-min interval between the end of facial immersion and the commencement of the 5-min baseline period of the next condition. Thus there was a 20-min interval between dives.

Session 2. Subjects reported to the laboratory and were fitted with an esophageal thermocouple and the skin heat flow sensors before a 5-min baseline recording of T_{es}, $\bar{T}_{sk}$, HR, SkBF, and MAP was performed. The subjects then performed 15 min of exercise on the treadmill at a work rate equivalent to 75% of their predetermined $\dot{V}O_{2\,max}$. This intensity has previously been reported to be effective in eliciting PEH (23, 25). After exercise, the subjects were seated in the upright position until $\bar{T}_{sk}$ returned to preexercise values and a plateau in elevated T_{es} was observed. That is, facial immersion was initiated when $\bar{T}_{sk}$ had returned to preexercise values, and when T_{es} and cardiovascular measures were stable. The stabilization of $\bar{T}_{sk}$, T_{es}, and cardiovascular measures occurred within 15–20 min postexercise and was consistent with the results of Kenny and Neidre (23).

Data Analysis

A 30-s resting average was calculated before any of the conditions were administered. The 30-s period between 60 and 30 s before facial immersion was used to calculate average baseline values of MAP, SkBF, and HR. An average relative value of the last 10 s of facial immersion was calculated for MAP and SkBF for comparison of total effect between conditions. However, an average relative value for each 5-s period during facial immersion was also calculated to show the time course of the response under each condition (3). The relative change from baseline was calculated for MAP and SkBF. For HR, however, only absolute values were also calculated for each 5-s period during facial immersion as well as an average value during the last 10 s of immersion. All values represent means ± SE for six subjects. A paired Student's *t*-test was used for statistical analysis with differences being considered significant at $P < 0.05$.

RESULTS

The HR reached during the last 10 s of immersion was significantly different from baseline under all conditions ($P < 0.05$; Figs. 2 and 3). The average HR nadir measured during the last 10 s of immersion for LBNP (61 ± 1 beats/min) and PEH (80 ± 2 beats/min) was different from both LBPP (46 ± 2 beats/min) and control (47 ± 1 beats/min) ($P < 0.05$; Table 2). The onset of bradycardia occurred at different times during immersion. Control HR became significantly different from baseline at 10 s followed by PEH and LBNP at 15 s and then LBPP at 20 s (Fig. 3).

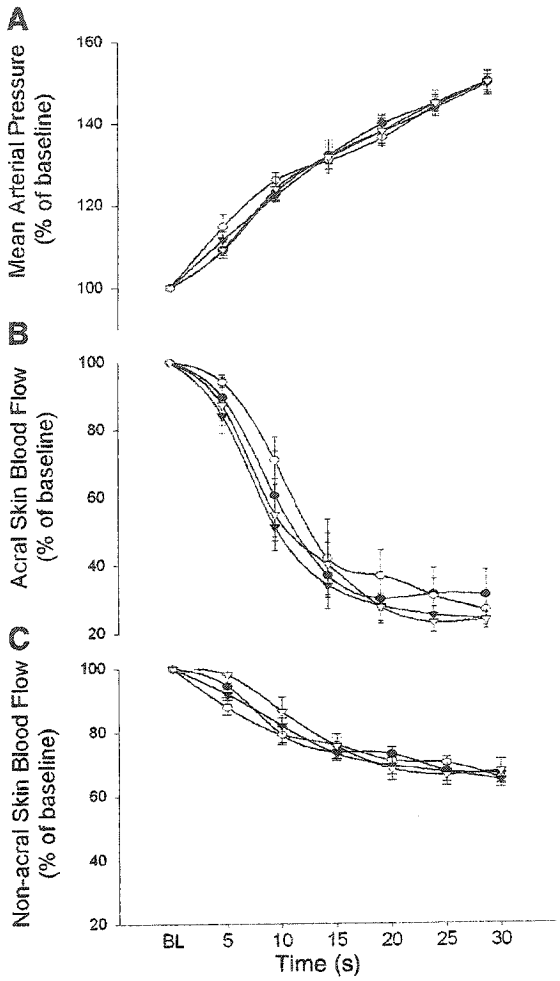

Fig. 2. Relative change from baseline for mean arterial pressure (*A*), acral skin blood flow (*B*) and nonacral skin blood flow (*C*) for the control (▽), PEH (▼), LBNP (○), and LBPP (●) treatment conditions for each 5-s interval during the 30-s facial immersion. Values are means ± SE for each 5-s interval for 6 subjects.

Each of the three conditions applied caused significant changes in HR from baseline resting before immersion ($P < 0.05$; Table 2). Thus the application of LBPP caused a 15 ± 1 beats/min decrease in HR, whereas LBNP and PEH caused a 9 ± 1 and a 13 ± 2 beats/min increase, respectively. Exercise also caused a 0.54 ± 0.11°C ($P < 0.05$) elevation in T_{es} from preexercise values that remained elevated during the time in which immersion was performed. MAP increased ~45–50% from baseline during immersion for all conditions ($P < 0.05$; Fig. 2*A*; Table 1). Exercise was effective in inducing PEH with a MAP decrease of 4.9 ± 0.6 mmHg compared with preexercise resting baseline ($P < 0.05$).

A marked reduction in SkBF was observed for all immersions at both the acral and nonacral sites ($P < 0.05$; Fig. 2, *B* and *C*; Table 1); however, there were no differences among conditions. The magnitude of the

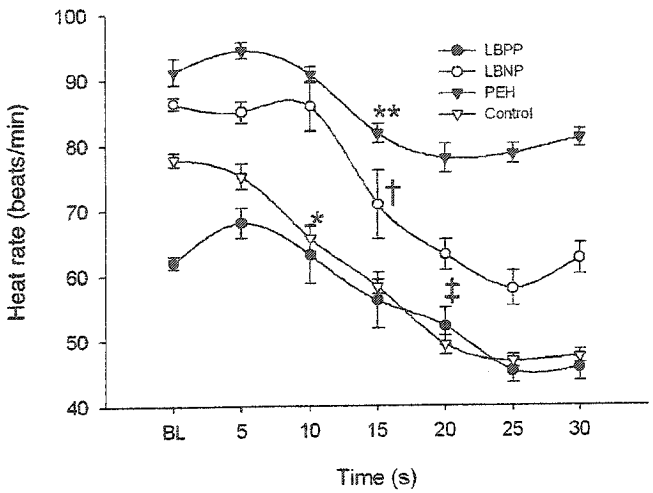

Fig. 3. Absolute heart rate responses during 30-s facial immersion for each 5-s interval for the control, PEH, LBNP, and LBPP treatment conditions. Values are means ± SE for each 5-s interval for 6 subjects. Times in which values became significantly different ($P < 0.05$) from baseline are denoted as follows: *control, **PEH, †LBNP, and ‡LBPP.

reduction in flow was much greater at the acral than the nonacral site with reductions of ~72 and ~33%, respectively, for all conditions ($P < 0.05$; Fig. 2, *B* and *C*; Table 1).

DISCUSSION

This study was unique in examining the diving response during altered cardiac filling subsequent to modification by lower body pressure and exercise. The most important finding was that various conditions that reduce cardiac filling do attenuate diving bradycardia. The diving response was produced in each of the four conditions applied in this study; however, the pattern and magnitude of the responses differed significantly. These results support previous postulates that diving bradycardia may be attenuated due to reduced cardiac filling either as a result of exogenous heat stress (5) or as a result of high intrathoracic pressure (1).

During LBNP (7, 9) and PEH (29), efferent sympathetic activity is increased through a baroreflex arc to maintain peripheral vascular resistance, whereas during LBPP (13), cardiac parasympathetic activity is increased. Both apnea and cold stimulation by the water promote chronotropic parasympathetic stimulation via the vagus nerve (2). Thus performing apneic facial immersion during LBNP or PEH sets up two independent stimuli that give rise to conflicting inputs of a common effector at the level of the brain stem. Our results suggest that when sympathetic efferent activity to the heart is increased because of reduced cardiac filling, diving bradycardia is attenuated. As a result of increased efferent sympathetic activity, the diving induced parasympathetic response is either inhibited or attenuated, thus reducing the bradycardia observed. In addition to the previously mentioned influences on the diving response, it is important to note that feedback as a result of respiratory muscle inhibition and chemoreceptor stimulation is a key component of the response (14). It was assumed that such influences were not altered by the experimental variables used in our protocol. Feedback subsequent to respiratory muscle inhibition and chemoreceptor stimulation was considered to be standardized in our study with each dive being limited to 30 s.

Table 1. *Mean percent change from predive baseline to mean value measured during last 10 s of immersion*

	Control	LBNP	LBPP	PEH
MAP	+47 ± 3	+47 ± 3	+47 ± 2	+48 ± 2
SkBF				
Acral	−77 ± 3	−71 ± 5	−69 ± 8	−74 ± 3
Nonacral	−33 ± 3*	−32 ± 4*	−32 ± 2*	−34 ± 3*

Values are means ± SE given in % for 6 subjects. LBNP, lower body negative pressure; LBPP, lower body positive pressure; PEH, postexercise hypotension; MAP, mean arterial pressure; SkBF, skin blood flow. *Significant difference from acral skin blood flow reduction, $P < 0.05$.

Facial immersion during PEH resulted in the greatest attenuation in diving bradycardia. During PEH, not only is preload compromised as a result of blood pooling in the previously active musculature (15, 23, 24) but also systemic hypotension exists (16, 17). It is reasonable to assume that the magnitude of the cardiac efferent sympathetic activity generated during systemic hypotension (29) would be greater than that generated by cardiopulmonary baroreceptor unloading with no change in MAP. It is possible that because of this greater magnitude of cardiac sympathetic outflow during PEH that diving bradycardia showed a greater attenuation than with LBNP.

Although reducing cardiac filling resulted in an attenuation of bradycardia, increasing cardiac filling with LBPP did not amplify bradycardia beyond that of the control condition. In order for the heart to maintain cardiac output at low HR values, stroke volume must be increased. It is known that during diving bradycardia cardiac output falls because stroke volume cannot compensate totally for the reduction in HR. In the resting seated position with LBPP of +40 mmHg used in this study, stroke volume is maximized (28); therfore, regardless of increased cardiac filling, the magnitude of bradycardia may have been limited to maintain

Table 2. *Absolute heart rate values*

	Control	LBNP	LBPP	PEH
Precondition	78 ± 1	77 ± 1	77 ± 1	78 ± 2
Baseline		86 ± 1*	62 ± 1*	91 ± 2*
Last 10 s	47 ± 1†	61 ± 1†	46 ± 2†	80 ± 2†

Values are means ± SE given in beats/min for 6 subjects. Baseline measurements represent the effect of the experimental condition on heart rate before immersion. Mean heart rates during the last 10 s of immersion are also shown. *Significant difference from resting precondition heart rate, $P < 0.05$. †Significant difference from baseline, $P < 0.05$.

an adequate cardiac output. The use of LBPP in this study was thought to attenuate cardiac sympathetic activity; however, it is important to consider the possibility that in the population studied tonic sympathetic activity was low or negligible and thus LBPP had no effect on diving bradycardia.

It should be noted that our control immersion produced the greatest effect on HR and that this effect was consistent with other studies using the same immersion time and similar water temperature (5, 6). At the other extreme, however, PEH exhibited the smallest bradycardic effect. However, the HR effects under the LBPP and LBNP conditions were also very different (Table 2). The average HR recorded in the last 10-s of immersion was very specific to each condition. As depicted in Fig. 3, HR values stabilized at higher values when cardiac filling was compromised during LBNP (61 ± 1 beats/min) and PEH (80 ± 2 beats/min) compared with the much lower rates achieved during LBPP (46 ± 2 beats/min) and control (47 ± 1 beats/min). This suggests that there is a mechanism that allows some of the diving-induced parasympathetic stimulation to act on the heart but that there is a point at which sympathetic drive dominates control of HR. Any mechanism that modifies arterial blood pressure can, through the negative-feedback loop of the baroreflex mechanism, influence HR (7). Thus the increased cardiac sympathetic activity during PEH (29) and LBNP (7) appears to dominate the afferent stimulus from facial immersion presumably through a baroreflex. On the basis of our results, this influence is more pronounced during greater cardiovascular stress; that is, PEH > LBNP > control = LBPP.

In this study, we also investigated the differences in cutaneous blood flow in acral (hand) and nonacral (forearm) regions during cutaneous vasoconstriction. In acral regions, cutaneous arterioles are innervated only through noradrenergic sympathetic nerves, and thus reflex changes, whether thermoregulatory or nonthermoregulatory, are mediated by adjustments in vasoconstrictor tone (21). Nonacral skin, however, includes both a noradrenergic vasoconstrictor system (both α_1- and α_2-receptors) and a separate active vasodilator system still under investigation (11, 12, 32). Whereas nonacral skin possesses two sympathetic neural pathways, the active vasodilator system is thought to play a prominent role during heat stress (21). To our knowledge, the potential differences between these two regions of skin have not been examined during facial immersion. Our data showed a greater percentage reduction in acral blood flow (~72%) than nonacral (~33%) when comparing either absolute values or when values were normalized to maximal cutaneous vascular conductance (data not shown). The results show that peripheral vasoconstriction was produced in both skin regions, but the reason for the greater percent reduction in acral skin is not completely clear. Further investigation is required to examine the differences between acral and nonacral regions. Specifically, it should be examined under conditions where blood flow levels during predive baseline are nearly equal between regions.

When examining the results globally, the fact that the experimental conditions resulted in an altered HR response but did not affect reductions in SkBF or the rise in MAP is noteworthy. Arnold and Nadel (5, 6) suggested that peripheral vasoconstriction is a requirement for diving bradycardia and noted that there is a relatively linear relationship between HR changes and changes to forearm blood flow. However, Finley et al. (10) previously concluded that the pharmacologic blockade of vasoconstriction and the increase in MAP did not affect the reflex diving bradycardia. Thus the peripheral vasoconstriction and rise in MAP are not essential for diving bradycardia to occur but are merely coincidental (10). Our results show that despite the varying degrees of bradycardia as a result of the experimental conditions, the acute reduction in SkBF and rise in MAP were unaffected. This observation supports the idea that although both parasympathetic and sympathetic efferents are activated during facial immersion, the responses they effect are independent of each other.

The results show that reducing cardiac filling pressure and, to a greater extent, inducing mild hypotension through exercise will attenuate the cardiac parasympathetic effects normally exhibited during facial immersion. The fact that peripheral blood flow and MAP changes were not different between conditions supports the idea that, during facial immersion, cardiac and peripheral responses are exerted separately.

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