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POTENTIAL CAUSES AND MECHANISMS OF POST EXERCISE HYPOTENSION

By

JAY R. MacDONALD

A Thesis

Submitted to the School of Graduate Studies

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Dedication

To my parents. I can never express the thanks I feel for your love, support and education in life. I hope and strive to continue to make you proud.

ABSTRACT

This thesis consists of five studies, conducted with the objective of advancing our understanding of post exercise hypotension (PEH) and its mechanisms. Studies 1, 2 and 3 examined the effects of exercise intensity (30 min of cycle ergometry at 50 and 75% $\dot{V}O_{2\ Peak}$), exercise duration (10, 15, 30 and 45 min of cycle ergometry at 70% $\dot{V}O_{2\ Peak}$) and the effects of exercising muscle mass (arms vs. legs) on PEH. In all cases, blood pressure was lower after exercise and the magnitude of this decrease was unaffected by the variations in protocol. Heart rate and $\dot{V}O_2$ were elevated through much of the hypotensive period in these studies, suggesting that a decrease in total peripheral resistance mediated the blood pressure effect as opposed to a decrease in cardiac output.

Study 4 was conducted to determine whether or not the hypotension following exercise is maintained during normal simulated activities of daily living (ADL). This study demonstrated a relative PEH, which persisted for at least 70 min of ADL. Systolic (SBP), diastolic (DBP) and mean (MAP) blood pressure were significantly decreased following exercise as compared to the non-exercise trial as well as from baseline measures. From this study, it can be concluded that acute exercise has the potential to serve as a non-pharmacological aid to hypertension.

Study 5 was conducted to determine the possible role of the central serotonergic system as a cause of PEH. While taking a placebo or selective serotonin reuptake inhibitor (SSRI) (randomised order) participants completed 30 min of cycling at 70% of $\dot{V}O_{2\ Peak}$. Peripheral measures of serotonin (5-HT) were decreased during SSRI treatment, whereas 5-hydroxyindoleacetic acid, was not statistically increased, suggesting elevated central 5-HT levels. However, the significant decrements in blood pressure

were similar between trials indicating that the central serotonergic system was not responsible for PEH in a borderline hypertensive population.

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And of course, my family – immediate and extended, who have shared in the successes and failures of life and supported me with encouragement, trust and love. Thank you.

PREFACE

The following is a list of abbreviations and operational definitions used throughout this thesis:

5-HIAA – 5-hydroxyindoleacetic acid
5-HT – serotonin (5-hydroxytryptamine)
5-HTP – 5 hydroxytryptophan
8-OH-DPAT – 8-hydroxy-2-(di-n-propyl-amino)tetralin
ACE – angiotensin converting enzyme
ACTH – adrenocorticotropin
ADH – antidiuretic hormone
ADL – activities of daily living
ANOVA – analysis of variance
ANP – atrial natriuretic peptide
BL – baseline
BP – blood pressure
BPM – beats per minute
C – Celsius
CAC – cardio-acceleratory centre
CIC – cardio-inhibitory centre
cm – centimetres
CO_2 – carbon dioxide
D – during
df – degrees of freedom
DHBA – dihydroxybenzylamineDBP – diastolic blood pressure. The lowest point of the arterial pressure waveform.
ECG – electrocardiogram
EDTA – ethylenediaminetetraacetic acid
F – female
FFT – fast fourier transformation
h – hours
H^+ - hydrogen ion
Hct – Haematocrit. The percentage of blood that is cells.
HF – high frequency (>0.15 Hz)
HPLC – high pressure liquid chromatography
HR – heart rate
HRV – heart rate variability
HSD – honestly significant difference
Hz – hertz
K^+ - potassium
kg – kilogram
Km/h – kilometres per hour
LF – low frequency (<0.15 Hz)
M – male
MAO – mono-amine oxidase

MAP – mean arterial pressure. The quotient of the integrated blood pressure and the duration of the time interval over which that blood pressure occurred.
MS – mean sums of squares
μL – microlitre
mg – milligram
mL – millilitres
mM – millimolar
mmHg – millimetres of mercury
Na^+ - sodium
O_2 – oxygen
pCPA – parachlorophenylalanine methylester HCl
PEH – post exercise hypotension. A transient decrease in blood pressure following an acute bout of exercise.
PG – prostaglandin
PNS – parasympathetic nervous system
PP – pulse pressure. The difference between systolic and diastolic blood pressure.
PSH – post stimulatory hypotension. A transient decrease in blood pressure following electrical stimulation of specific nerves or muscles.
$\dot{Q}c$ - cardiac output. The product of heart rate and stroke volume.
RM – repetition maximum
RPM – revolutions per minute
RPP – rate pressure product. The product of heart rate and systolic blood pressure divided by 1000.
s – seconds
SBP – systolic blood pressure. The highest point in the arterial pressure waveform.
SD – standard deviation
SEM – standard error of the mean
SNA – sympathetic nerve activity
SNS – sympathetic nervous system
SSRI – selective serotonin reuptake inhibitor
SV – stroke volume. The volume of blood ejected from the heart during contraction.
TPR – total peripheral resistance. The quotient of mean arterial pressure and cardiac output.
VCC – vasomotor control centre
$\dot{V}O_2$ - oxygen consumption
$\dot{V}O_{2Max}$ - maximal oxygen consumption reached during progressive treadmill running.
$\dot{V}O_{2Peak}$ - maximal oxygen consumption reached during progressive arm or leg ergometry.

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CHAPTER 1

An Overview Of Blood Pressure Regulation

1.1 INTRODUCTION

The major function of the cardiovascular system is to provide the appropriate blood flow to tissues and organs. This includes maintaining flow to vital organs such as brain and heart and adjusting flow to other tissues and organs to meet changes in metabolic demands. This function is achieved by maintaining or altering mean arterial blood pressure and by regionally distributing blood flow through adjustments in vascular resistance. This chapter will attempt to summarise the mechanisms involved in human blood pressure control and their interactions.

In its simplest analysis, at any given point in time, arterial blood pressure is determined by the amount of blood in the systemic arterial "tree" (i.e. cardiac output) and the total peripheral resistance (the summed effect of the average radii of the arterioles in each vascular bed). As can be seen in figure three and as will be discussed in this chapter, this statement is an oversimplification, since the two variables are not independent. In addition, there are a number of mechanisms that can affect and control these variables and a complete understanding is complicated by the many different ways by which these mechanisms can interact. The process is further complicated by the fact that a number of mechanisms perform the same function and this "redundancy" makes it difficult to experimentally isolate and examine mechanisms separately.

1.1.1 Hypertension

Hypertension is a condition of high blood pressure. It knowingly affects approximately 10% of the adult population and is often termed the "silent killer" since there are generally no obvious symptoms. Hypertension can lead to a variety of conditions including stroke, congestive heart failure and heart attacks (Tipton, 1984).

Hypertension can be classified into two categories – essential hypertension and secondary hypertension. Essential hypertension has no known causes and accounts for the majority of cases. Conversely, secondary hypertension results from known conditions, generally in the endocrine or vascular systems.

1.2 RAPID AND SHORT TERM CONTROL OF BLOOD PRESSURE

1.2.1 The Autonomic Nervous System

Sympathetic nervous system (SNS) stimulation can have pronounced effects on blood pressure. A variety of stimuli including chemical, emotional and physical factors can alter sympathetic outflow. Two such sympathetic reflexes, namely the baroreceptors and chemoreceptors, will be discussed in greater detail below. Sympathetic nerve fibres innervate virtually all blood vessels of the body, with the exception of the capillaries and their associated pre-capillary sphincters (Guyton & Hall, 1996). Activation of the SNS causes the secretion of norepinephrine at the nerve endings to generally achieve vasoconstriction. On the arterial side, this vasoconstriction causes an increase in peripheral resistance while on the venous side it causes a transfer of blood from the venous circulation to the heart and arterial circulation, therefore increasing blood pressure throughout the body. Generally, the secretion of norepinephrine at the SNS nerve endings achieves vasoconstriction. This norepinephrine acts predominantly on peripheral alpha-receptors. The degree of vasoconstriction via alpha-receptor stimulation is tissue dependent. The kidney, spleen and skin are known to be highly sensitive to alpha-receptor stimulation, whereas skeletal and cardiac muscle are not. In humans, skeletal muscle is also innervated by a number of sympathetic vasodilator fibres in addition to the constrictor fibres. However, the extent of vasodilation in the muscle beds is minimal via

this mechanism and is mostly controlled by local and hormonal factors as discussed below (Guyton & Hall, 1996).

In addition to the generalised vasoconstriction, SNS stimulation also causes increases in both heart rate and contractility, which increase cardiac output, which on its own also increases arterial pressure. It has recently been shown that hypertensive individuals have increased basal sympathetic nerve activity suggesting that their hypertension may be due to augmented sympathetic outflow (Grassi, 1998).

1.2.2 Baroreceptors

The baroreceptors are one of the most important mechanisms in blood pressure regulation. These receptors are located in the walls of the aortic arch and the carotid arteries at the level of the carotid sinus. These areas are sensitive to changes in stretch and pressure. As indicated in figure one, the baroreceptors have direct afferent projections to the medullary area of the brain controlling cardiovascular activity and work as an immediate feedback control loop in blood pressure regulation. As blood pressure increases, the baroreceptors increase their rate of discharge to those medullary neurons that have a cardio-inhibitory function. This results in increased vagal (parasympathetic) output to the heart and decreased sympathetic stimulation to the heart and blood vessels, causing vasodilation and a decreased heart rate and force of contraction, thus decreasing cardiac output and vascular resistance in an attempt to return blood pressure to normal. A decrease in blood pressure will elicit opposite results. Although the aortic and carotid baroreceptors function in parallel, the carotid baroreceptors respond maximally to changes in mean arterial pressures between 60 and 180 mmHg, whereas the aortic

baroreceptors respond most rapidly to pressure changes between 90 and 210 mmHg (Guyton and Hall, 1996).

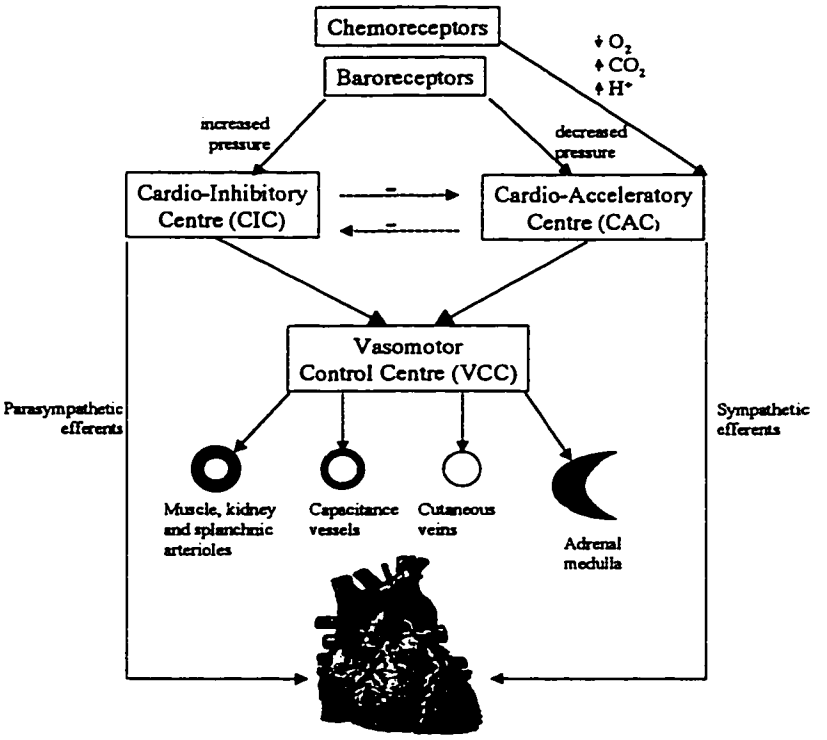

Figure 1. A schematic representation of cardiovascular control.

The baroreceptors have been found to operate more efficiently in response to a **change** in pressure as opposed to the static pressure *per se* (Berne & Levy, 1988). Changes in static blood pressure will cause the baroreceptors to "reset", and transmit nerve impulses based on pressure changes around the new "set point", suggesting little role of the baroreceptors in long term control of blood pressure (Cowley, 1992). Substantially increased or prolonged activity of the arterial baroreceptors also directly causes the release of antidiuretic hormone (ADH) via nerve connections to the hypothalamic nuclei that control ADH production and release. The role of ADH in blood pressure regulation will be discussed below.

1.2.3 Chemoreceptors

Situated in close proximity to the baroreceptors in the carotid bodies and aortic arch are the arterial chemoreceptors. These specialised cells are able to sense changes in hydrogen ion concentration, oxygen concentration and most effectively, carbon dioxide concentration. As blood pressure falls, carbon dioxide and hydrogen ion concentrations will increase whereas oxygen concentration will decrease due to the diminished blood flow (Guyton, 1980). As with the baroreceptors, these chemoreceptors have direct projections to the cardiovascular control centre to effect reflexive changes in innervation of the blood vessels and cardiac muscle, thus returning blood pressure to normal. Working in concert with the baroreceptors, the chemoreceptors respond maximally to chemical changes that would be evident with mean arterial pressures below 80 mmHg (Guyton & Hall, 1996).

1.2.4 Circulating Catecholamines

In response to direct sympathetic stimulation, the adrenal medullae secrete norepinephrine and epinephrine. Their effects are summarised below.

1.2.4.1 Norepinephrine

Circulating norepinephrine affects arterial pressure in a similar manner as discussed above, by its effects on alpha receptors, usually causing vasoconstriction in most vascular beds (Barcroft et al., 1954). In fact, some of the circulating norepinephrine is "spill over" from sympathetic nerve endings, thus elevating the blood concentrations above that released from the adrenal medullae. The effects of this "spill over" and the norepinephrine released from the adrenal medullae persist longer than that released at the SNS nerve endings due to its relatively slow removal rate from the circulation.

1.2.4.2 Epinephrine

Epinephrine binds to both alpha and beta receptors. Stimulation of the alpha receptors will cause vasoconstriction, as with norepinephrine. However, epinephrine will also bind to beta receptors, predominantly in skeletal muscle beds, to cause marked vasodilation (Guyton & Gillespie, 1951). Additionally, epinephrine has a direct effect on cardiac beta receptors to increase the rate and force of contraction of the heart. The effects of vasodilation and increased cardiac output have independently opposite effects on blood pressure, but are necessary to increase cardiac output while supplying adequate blood flow to working muscles during periods of stress or exertion.

1.2.5 Potassium (K^+) and Adenosine

Potassium (Morganroth et al., 1977) and adenosine (Belloni et al., 1979) are both known to exhibit strong dilatory effects on vascular smooth muscle. Some have hypothesised that K^+ and / or adenosine are primarily responsible for the reactive hyperemia during exercise. It is doubtful that K^+ or adenosine has any effect on the resting tone of the vascular system.

1.3 INTERMEDIATE AND LONG TERM CONTROL OF BLOOD PRESSURE

1.3.1 Factors Directly Affecting Blood Volume

The vast matrix of factors that control blood pressure include many direct and indirect variables. Two of the most prominent factors affecting blood pressure are the sodium concentration and the capillary shift mechanism that controls blood volume and, in turn, pressure.

1.3.1.1 Sodium (Na^+)

Blood volume *per se* is an integral factor in maintaining blood pressure. One of the major influencing factors of blood volume is the concentration of extracellular Na^+. As Na^+ accumulates within the body, the osmolarity also increases. This increase in osmolarity stimulates thirst in an effort to decrease the heightened Na^+ concentration, and, therefore results in an increased extracellular fluid volume. The stimulation of thirst comes from direct effects of increased osmolarity on the central thirst centre as well as stimulation of the posterior pituitary gland to secrete increased quantities of ADH (Guyton, 1980). The result of elevated ADH levels is an increase in blood volume by the mechanisms discussed below.

1.3.1.2 Capillary Shift Mechanism

The capillary shift mechanism is a simple, but effective, regulator of blood volume. In the simplest view, barring any changes in osmotic pressure, if the pressure in the capillaries is increased substantially, the increase in pressure drives fluid out of the circulation and into the tissues. This diminishes the blood volume and, therefore, decreases blood pressure. Conversely, if the pressure in the capillaries decreases, fluid is absorbed from the surrounding tissue, increasing blood volume and, in turn, blood pressure. The capillary shift mechanism is an effective buffer for changes in blood pressure, as might result from alterations in posture or physical activity. It requires approximately 15 min to two hours to achieve its full pressure buffering capacity (Guyton, 1980).

1.3.2 Renal Control Of Blood Pressure

The kidneys are important in both short and long term regulation of blood pressure. At rest, the kidneys receive approximately 20% of cardiac output (Guyton, 1980). Although the exact mechanisms of kidney regulation are not completely understood, it appears as though the juxtaglomerular apparatus is responsible for a high degree of autoregulatory function in fluid regulation and blood pressure. For over a century it has been known that efferent nerve activity can cause renal vasoconstriction and, therefore, significant reductions in renal blood flow (Bradford, J.R., 1889), causing decreased urine output and sodium excretion. Only over time have we been able to better understand the other renal mechanisms involved in the control of blood pressure. It is now generally accepted that the renal systems involved in blood pressure regulation, as discussed below, are the most sensitive control mechanisms, but are mostly responsible for long term regulation of pressure.

1.3.2.1 Renin Angiotensin System

One of the more powerful blood pressure regulating mechanisms is the renin angiotensin system. A schematic diagram of this system is presented in figure two. Briefly, the juxtaglomerular cells of the kidney produce inactive molecules of prorenin. Upon detection of low perfusion pressure, salt deficiency, dehydration or enhanced renal sympathetic stimulation, prorenin is cleaved and released into the circulation as renin. Renin circulates in the blood with a long half life of ~20 min before being completely catabolised by the liver (Stroth & Unger, 1999). Renin, acting as an enzyme, cleaves the liver produced, circulating angiotensinogen to form angiotensin I. This angiotensin I has very mild vasoactive properties. Renin release from the kidneys is the rate limiting factor

in the conversion of angiotensinogen to angiotensin I. Angiotensin converting enzyme (ACE), found in high concentration in lung capillary tissue, cleaves angiotensin I to form angiotensin II as it passes through the capillary tissue of the lungs. It is this angiotensin II that has strong vasoconstrictive properties. This vasoconstriction can occur within minutes of the activation of the renin angiotensin system and functions as an intermediate factor in blood pressure control (Stroth & Unger, 1999). Although the lungs are the major site of angiotensin converting enzyme, minute quantities have been found in other tissues, including the kidneys, suggesting that an intra-renal renin angiotensin system may play a significant role in the local control of renal arteriolar activity (Guyton, 1980). Throughout the body, vasoconstriction is caused by the binding of angiotensin II to specific vascular receptors causing an increase in intracellular calcium concentrations (Stroth & Unger, 1999). Angiotensin II has also been demonstrated to increase sympathetic nerve activity and cardiac contractility and stimulate thirst, further exerting its effects on the rapid and intermediate control of blood pressure (Zimmerman et al., 1984; Navar, 1997).

As a long-term moderator of blood pressure regulation, angiotensin II exerts its effects on the kidneys, inducing water and salt retention. In addition to the systemic effects of angiotensin II, it has recently been shown to bind to receptors in the hypothalamus, causing the release of antidiuretic hormone (Hoehle et al., 1995).

Angiotensin II is rapidly degraded as it travels through the blood stream and through peripheral tissues. Therefore, its concentration is significantly greater in the arterial blood.

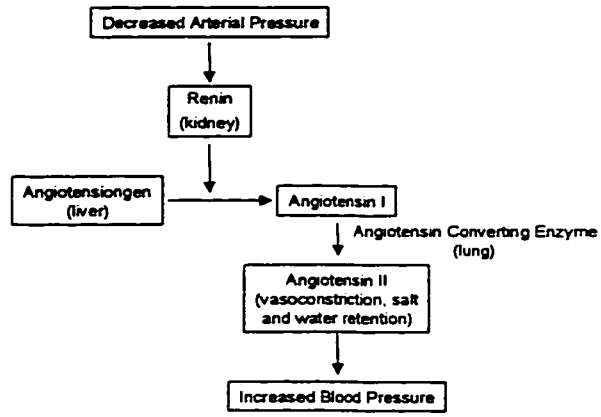

Figure 2. A basic schematic of the renin-angiotensin system.

1.3.2.2 Aldosterone

Closely linked to the renin-angiotensin system is the steroid hormone aldosterone. Aldosterone is produced and released from the adrenal cortex in response to increasing levels of angiotensin II, and perhaps to one of its break down products, angiotensin III (Guyton, 1980). Additionally, aldosterone can be secreted in response to increased plasma K^+ concentration (Guyton, 1980), and to a lesser extent, decreased plasma Na^+ concentration (Yu & Morris, 1997) or the concentration of circulating adrenocorticotropin (ACTH) (Otsuka et al., 1998). Aldosterone has powerful Na^+ and water retention actions on the kidney and acts over hours or days in concert with the renin-angiotensin system for long term control of blood pressure.

1.3.2.3 Antidiuretic Hormone (Vasopressin)

Working in conjunction with the kidney, but released from the posterior pituitary gland, antidiuretic hormone is a key contributor in regulating the concentration of Na^+ and osmolarity in the extracellular fluid. During periods of fluid depletion, when osmolarity increases, specific "osmoreceptors" in the anterior hypothalamus detect the increased sodium concentration, causing them to transmit nerve impulses to the posterior pituitary. This increased nerve activity causes the release of antidiuretic hormone (Hays, 1996). Upon reaching the kidneys, the antidiuretic hormone causes increased water permeability at the distal tubule and collecting duct, and therefore, increased water re-absorption (Jard, 1998).

Antidiuretic hormone also has been found to be increased in response to decreases in blood pressure and volume. However, changes of the hormone are minimal to these stimuli compared to the changes in response to alterations in osmolarity. The antidiuretic hormone pathway is considered to be one of the fastest acting of the intermediate controls of blood pressure, often having significant effects within several minutes (Guyton, 1980).

1.3.3 Other factors

1.3.3.1 Prostaglandins

Prostaglandins are biologically active breakdown products of arachidonic acid via the cyclooxygenase cascade (Navar, 1997). There are a variety of prostaglandins within the body. Acutely, prostaglandins are released in response to vasoconstriction, volume depletion and hypoperfusion (Navar, 1997). Prostaglandins are closely intertwined with other blood pressure regulating systems and their formation can also be stimulated by catecholamines, angiotensin II and antidiuretic hormone (Smith, 1992). Release of

prostaglandins into the circulation can have a variety of effects, although most prostaglandins are known to cause vasodilation. Infusion of prostaglandins causes renal vasodilation, increased Na^+ excretion by the kidneys, and a rapid increase in renin secretion. Early work had suggested that the renal medullae may secrete prostaglandins into the circulation for persistent peripheral vasodilation (Guyton, 1980). This has not been confirmed in recent years.

1.3.3.2 Kallikrein Kinin System

Kallikrein is a proteolytic enzyme peptide present in most tissues of the body and in the circulation. Once kallikrein becomes activated, it is responsible for the release of kallidin from $alpha_2$-globulins. Soon after, kallidin is converted to bradykinin. Bradykinin is short lived and causes intense arteriolar dilation and capillary permeability, thus decreasing blood pressure and volume. It has been speculated that the renal system may influence the kallikrein kinin system since it is known to work in reciprocity with the renin angiotensin system by way of angiotensin converting enzyme (Stroth & Unger, 1999). Angiotensin converting enzyme, responsible for the conversion of angiotensin I to angiotensin II, is also responsible for the degradation of bradykinin. Bradykinin has also been demonstrated to interact with other vasoactive substances. It is suggested that bradykinin stimulates the formation of prostaglandin E_2 and I_2 (Carretero et al., 1987) as well as modulate the degree of vasoconstriction induced by norepinephrine. This latter mechanism is thought to be mediated by nitric oxide (Carretero et al., 1987; Mombouli & Vanhoutte, 1995).

1.3.3.3 Serotonin

Serotonin or 5-hydroxytryptamine (5-HT) is derived from the essential amino acid L-tryptophan (Weber & Horita, 1965). Only about 2% of the human daily intake of L-tryptophan is used to synthesize the approximately 10 mg of serotonin required by the human body each day (Levine, 1974). The synthesis of serotonin from tryptophan proceeds via two enzymatic reactions. Initially, tryptophan is converted to 5-hydroxytryptophan in the presence of the enzyme tryptophan hydroxylase. This is the rate limiting step of serotonin production. The second reaction in the production of serotonin is the conversion of 5-hydroxytryptophan to 5-hydroxytryptamine. This is accomplished in the presence of the enzyme L-aromatic amino acid decarboxylase. Unlike the specific tryptophan hydroxylase, L-aromatic amino acid decarboxylase is found in most tissues and will act in the decarboxylation of all aromatic amino acids (Zhu & Juorio, 1995).

Specific investigations of the effects of serotonin on the cardiovascular system have elicited interesting and often contradictory results. The effects appear to be site and species specific. Unfortunately, with the majority of serotonin acting in the brain centres, little work has been possible in the human model. The species specificity also makes extrapolation to humans difficult.

Investigations with the rodent model indicated that intraventricular injection of the serotonin precursor L-tryptamine causes no significant decrement in blood pressure and in some instances may elevate it in normotensive rats (Krstic & Djurkovic, 1985). However, intraperitoneal injection in spontaneously hypertensive rats has been shown to decrease blood pressure (Sved et al., 1982). In the cat model, intra-ventricular injection

of tryptophan, in the presence of a MAO inhibitor, elicited a 40-80% reduction in blood pressure (Florez and Armijo, 1974). In both the rodent and the cat model, the decrement in blood pressure has been found to be mediated by a decrease in preganglionic sympathetic nerve activity (Baum & Shropshire, 1975; Tadepalli et al., 1977).

Numerous researchers have targeted certain areas of the brain in an attempt to assess the specificity of serotonin and its effects on these centres. It has been noted that the medulla contains many serotonergic neurons. Electrical stimulation of this area leads to a decrease in peripheral blood pressure accompanied by a parallel decrease in sympathetic nerve discharge (Chalmer & West, 1983). Conversely, microinjection of serotonin into the anterior hypothalamus in normotensive and hypertensive rats elicits an increase in arterial blood pressure (Wolf et al., 1981; Robinson, 1971). The direct arterial pressure responses to serotonin in humans have not adequately been investigated. The literature suggests that in the hypertensive population, small amounts of serotonin introduced into the antecubital vein evoked slight decrements in pressure in the magnitude of 10/5 to 20/15 mmHg for systolic/diastolic pressure, respectively. Larger doses tended to elicit a triphasic response of hypotension, hypertension and prolonged hypotension (Page & McCubbin, 1953).

Due to the varied response across species and the inability to accurately measure central versus peripheral levels of serotonin in humans, further work is needed to deduce the contributions that serotonin may play in blood pressure regulation.

1.3.3.4 Nitric Oxide

Nitric oxide may be one of the most diverse and potent effectors of blood pressure, yet it is still poorly understood. It is believed that, in response to shear stress,

increased nitric oxide is released from the endothelial wall. This nitric oxide has a very short half life of approximately six seconds (Moncada, 1997), but causes marked relaxation of the arterial wall, and therefore decreases blood pressure. There is some experimental evidence to suggest that release of nitric oxide from the endothelial cells may also be stimulated by signals from sympathetic nerve endings (Boric et al., 1999). This may indicate that nitric oxide is responsible for maintaining a sympathetic "tone" of the vasculature and, therefore may play a significant role in both the acute and chronic control of blood pressure. Limited evidence indicates that, in addition to its direct effects, nitric oxide may also serve to decrease vascular responsiveness to other circulating mediators of blood pressure (e.g. catecholamines) (Patil et al., 1993).

1.3.3.5 Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) is one of the newly discovered blood pressure and volume regulating hormones. It is produced predominantly in the right atrium and is released in response to atrial stretch, either due to plasma volume expansion (Anderson et al., 1986) or enhanced venous return (Berlin et al., 1993). ANP has direct vasodilatory properties that may persist long after its 2-3 min half life. Additionally, ANP acts on the kidneys to decrease reabsorption of sodium and water in an attempt to return blood volume back to normal. There is also evidence to suggest that ANP inhibits renin, aldosterone and antidiuretic hormone (Cowley, 1992), all causing a decrease in cardiac output.

1.4 SUMMARY

Maintenance of blood pressure is an integral component of maintaining life. Substantial decrements in blood pressure can cause hypoperfusion that can lead to tissue

necrosis and ultimately death. Conversely, increased blood pressure heightens the risk of heart attack and stroke. It is therefore important to keep blood pressure tightly regulated. The primary mechanisms in the rapid, intermediate and long term control of blood pressure summarised here are tightly regulated and work in symbiosis to maintain optimal pressure and blood flow. Due to the degree of integration and redundancy in the blood pressure regulating mechanisms, failure of one is often adequately compensated for by a secondary control device. Many of the factors that determine blood pressure and their potential interactions are summarised in figure three.

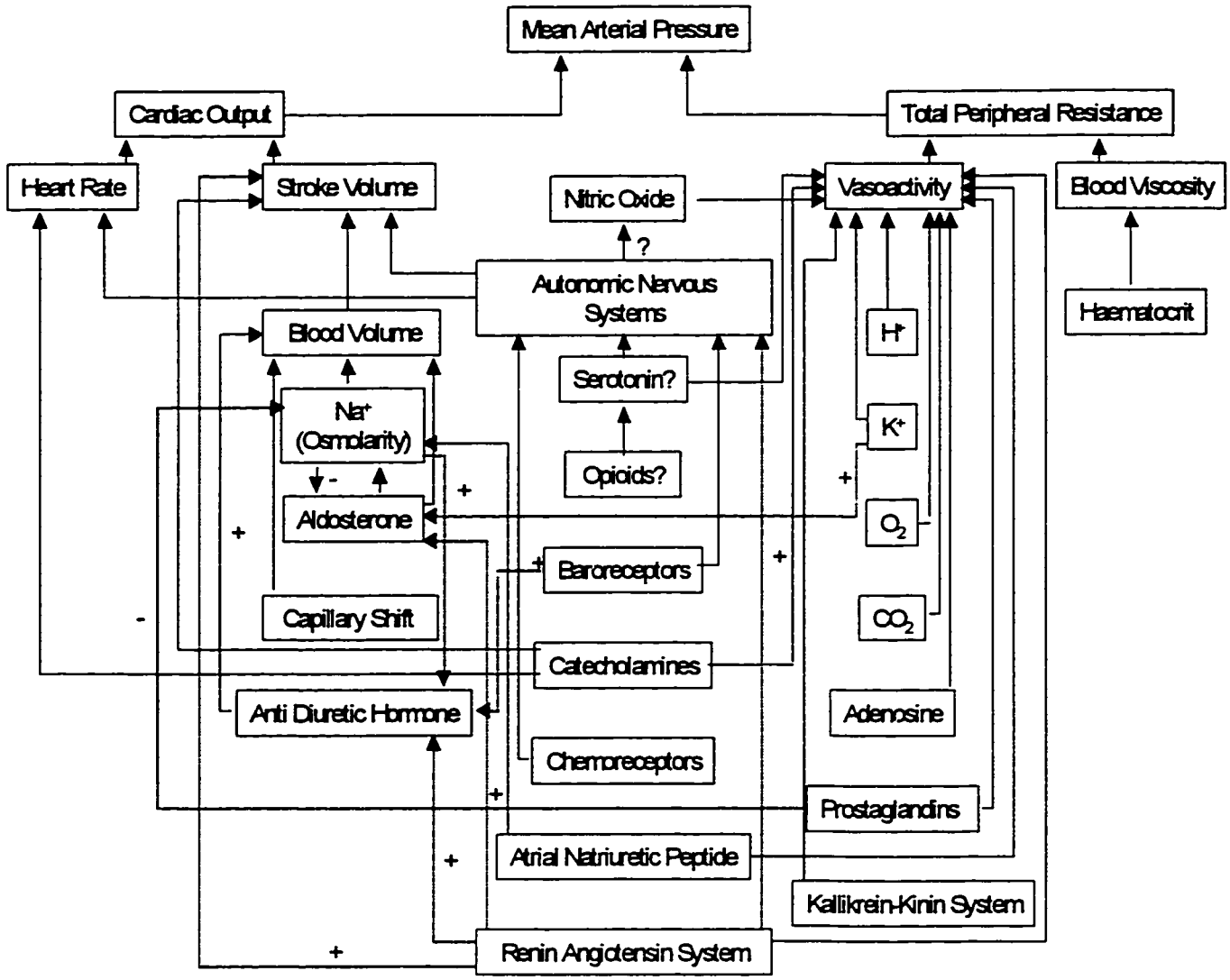

Figure 3. A schematic overview of blood pressure regulation.

CHAPTER 2

Blood Pressure, Exercise And Post Exercise Hypotension – A Review

2.1 BLOOD PRESSURE RESPONSES TO EXERCISE

During exercise, cardiac output increases dramatically to allow adequate perfusion of the working musculature. This increase is achieved by a reduction of parasympathetic tone (causing an increased heart rate and contractility), an increase in sympathetic activity (directly and indirectly increasing heart rate and contractility) and a pronounced vasoconstriction of the venous vasculature (causing a greater venous return and therefore stroke volume). In parallel, the need for an increased blood flow and oxygen delivery to the exercising muscle is achieved by a regional vasodilation of those arterioles supplying blood to exercising tissue combined with a vasoconstriction of arterioles which perfuse non-essential tissues. Although the cause of the local vasodilation at the onset of exercise is not fully understood, many of the vasodilatory factors (e.g. potassium, adenosine, NO, etc) summarised in the preceding chapter have been implicated in the local haemodynamic changes associated with exercise. Contraction of the active muscle mass also assists in returning blood towards the heart. This "muscle pump" effect further increases venous return and stroke volume.

The increased cardiac output and vasoconstriction in non exercising vascular beds increases systolic blood pressure, but the significant vasodilation at the exercising muscle beds helps to buffer this increase and results in a minimal rise in diastolic blood pressure. As exercise continues at the same intensity, blood pressure is often found to diminish from the peak values achieved early in exercise. This may be attributed to a redistribution of blood to the periphery for heat dissipation, and the resultant reduction in cardiac filling (MacDougall et al., 1974). Endurance and resistance exercise elicit

differences in their cardiovascular responses. These differences are discussed below and are summarised in figure four.

2.1.1 Endurance Exercise

With endurance type exercise (i.e. cycling, running), systolic blood pressure is tightly coupled to the exercise intensity and can often reach values of over 200 mmHg with maximal exercise (MacDougall, 1994). Although it is usually reported that diastolic blood pressure changes little throughout changes in the exercise intensity, Palatini (1994) has suggested that changes in diastolic blood pressure are more variable and can range from a slight decrease, due to the vasodilation of the muscle vasculature, to an increase of 10 to 20 mmHg, presumably from the occlusion of blood flow caused by the forceful contractions of the exercising muscle. Following exercise, blood pressure rapidly returns to normal. As shown in figure four, there is often a transient pressure undershoot caused by a pooling of blood in the dilated, previously exercising muscle beds. This pressure decrement in the minutes following exercise is more pronounced following intense exercise. The baroreceptors, as described in the previous chapter, work to counter the circulating vasodilatory substances to return homeostasis within 10 min following exercise.

2.1.2 Resistance Exercise

Resistance exercise (i.e. weight lifting) elicits more pronounced increments in both systolic and diastolic blood pressure. MacDougall et al. (1985) demonstrated average peak blood pressure values of 320/250 mmHg during the double leg press, in resistance trained volunteers, with some individuals reaching values of 480/350 mmHg. These large changes in blood pressure are due to the sum of sympathetic vasoconstriction

in non-exercising vascular beds, mechanical compression of the blood vessels in the exercising muscle beds and the Valsalva manoeuvre (a forced expiration against a closed glottis used to stabilise the trunk muscles during heavy weight lifting) which greatly increases intrathoracic pressure (MacDougall, 1994). The changes in blood pressure during resistance exercise are oscillatory and related to the phase of the lift. Blood pressure increases to maximal values as determined by the resistance encountered during the lifting phase. Pressures then decline, often to below resting values at the completion of the lift and then increases again during the lowering phase of the exercise (Lentini et al., 1993). As shown in figure four, the reattainment of baseline blood pressure values is similar to that of endurance exercise, although the transient pressure undershoot is often more pronounced following heavy resistance exercise.

2.2 BLOOD PRESSURE FOLLOWING EXERCISE

A number of investigators have examined the effects of chronic exercise training on resting blood pressure in hypertensive populations (see review by Tipton, 1999). It is generally accepted that the mechanisms underlying the sustained lowering of blood pressure in hypertensive individuals after training, are a decrease in the resting heart rate and a decrease in circulating catecholamines (Tipton, 1984). This decrease in circulating catecholamines is directly related to a decrease in sympathetic nerve activity.

Acute studies examining the effects of exercise on blood pressure have noted the transient pressure undershoot, described above, but have normally been terminated when blood pressure has re-attained normal values. However, more recent studies examining blood pressure responses in the prolonged post exercise period have documented that an

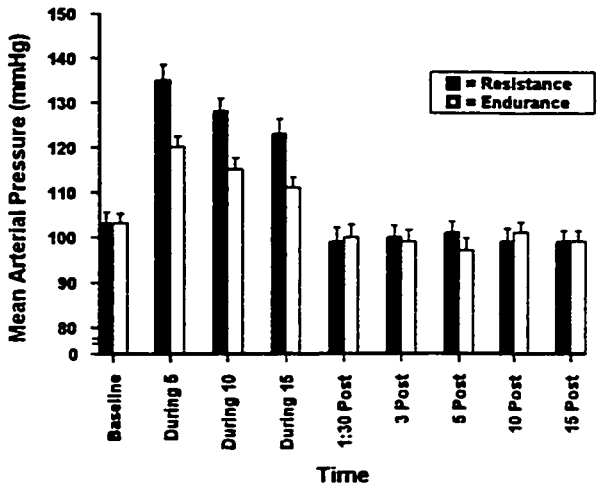

Figure 4. Mean blood pressure responses to endurance exercise (cycling at 65% $\dot{V}O_{2\,Peak}$) and resistance exercise (unilateral leg press at 65% 1RM). Data from reference 73 (MacDonald et al., 1999a).

acute bout of exercise may transiently decrease resting blood pressure in the minutes or hours following exercise (see review by Kenney & Seals, 1993). Although there are no defined criteria for the magnitude of the pressure decrement or duration of the response, this transient reduction in blood pressure has been termed post exercise hypotension (PEH). Post stimulatory hypotension (PSH) refers to the same phenomenon when it is elicited by simulating exercise by electrically stimulating muscles in certain animal models.

2.3 POST EXERCISE HYPOTENSION

Although PEH was first documented by L. Hill in 1897 (Hill, 1897) during the 90 min following a 400 yard dash, it was only after Fitzgerald's 1981 (Fitzgerald, 1981) anecdotal report of the effect of jogging, on his own labile hypertension, that the scientific community began to systematically examine this phenomenon. The purpose of

the following review is to summarise and integrate the current state of knowledge surrounding PEH/PSH.

2.3.1 Does PEH Occur In All Individuals?

PEH has been well documented in borderline hypertensive (e.g. Somers et al., 1985; Floras et al., 1989; MacDonald et al., 1999c) and hypertensive (e.g. Hagberg et al., 1987; Wilcox et al., 1987; Reuckert et al., 1996) humans. Its occurrence in normotensive humans is inconsistent. Although we have found that PEH can be detected in normotensive subjects (MacDonald et al., 1999a), in screening subjects as participants in the studies included in this thesis, it was found to be much less predictable and of lesser magnitude than in those subjects who tended to have higher than normal blood pressure. A possible explanation for this is that other compensatory mechanisms such as the baroreflex are activated in normotensive subjects, to prevent the degree of PEH from affecting orthostatic tolerance.

Although there are reports of gender differences in blood pressure (Hayward & Kelly, 1997) and sympathetic nerve activity (Matsukawa et al., 1998) PEH appears to be unaffected by gender, since gender specific (e.g. Paulev et al., 1984; Headley et al., 1996) and mixed gender studies (e.g. Coats et al., 1989; Raglin et al., 1993; Brown et al., 1994; Reukert et al., 1996) have found similar degrees of hypotension. It also occurs independent of age and has been observed in young (Kaufman et al., 1987; Southard & Hart, 1991), middle aged (Kaufman et al., 1987) and older adults (Hagberg et al., 1987). PEH/PSH has also been documented in normotensive (e.g. Yao et al., 1982a) and spontaneously hypertensive rats (e.g. Chen et al., 1995; Chandler & DiCarlo, 1997) and Dahl salt-sensitive rats (Kenney et al., 1991). Limited work suggests that PSH does not

occur in Dahl salt-resistant (Kenney et al., 1991) or renal hypertensive rats (Hoffmann & Thoren, 1986). Given the inconsistency of the PEH response in normotensive humans, the lack of hypotension found in these studies is not unexpected. It has been suggested that the degree of PSH may be related to the genetic pre-disposition of the animal to hypertension (Kenney et al., 1991). Further study is needed to examine the effects of genetic predisposition on PEH in the normotensive human population.

2.3.2 Magnitude Of The Blood Pressure Decline

The available literature suggests that the decrements in blood pressure are more consistent and of greater magnitude in borderline hypertensives and hypertensives than in normotensives. In those studies that did find a drop in blood pressure following exercise, the average maximal decrement in pressure was approximately 8/9 (SBP/DBP) mmHg in the normotensive population (Kaufman et al., 1987; Coats et al., 1989; Boone et al, 1992; Franklin et al, 1993; Piepoli et al., 1993; Raglin et al., 1993; Brown et al., 1994; Hara & Floras, 1994; Isea et al., 1994; Headley et al, 1996; MacDonald et al., 1999a), 14/9 mmHg in the borderline hypertensive population (Somers et al., 1985; Floras et al., 1989; Hara & Floras, 1995; MacDonald et al., 1999 b, c, d, e, f) and 10/7 mmHg in the hypertensive population (Hannum & Kasch, 1981; Hagberg et al, 1987; Kaufman et al., 1987; Pescatello et al., 1991; Cleroux et al., 1992; Hara & Floras, 1994; Brownley et al., 1996; Reukert et al., 1996; Wallace et al., 1999). Rodents generally experience a drop of greater magnitude than humans. Absolute decrements in mean arterial pressure between the two species are approximately 50% greater in hypertensive rodents than in hypertensive or borderline hypertensive humans (Yao et al., 1982a, b; Paulev et al., 1984; Hoffmann & Thoren, 1986, 1988; Overton et al., 1988; Hoffmann et al., 1990a, b;

Pescatello et al., 1991; Collins & DiCarlo, 1993; Chen et al., 1995; VanNess et al., 1996; Reukert et al., 1996; Chandler & DiCarlo, 1997; Silva et al., 1997; Kulics et al., 1999; MacDonald et al., 1999b, c, d, e, f;)

2.3.3 The Effect Of Variations In Exercise On PEH

2.3.3.1 Type Of Exercise

PEH has been noted after a variety of aerobic type exercise including walking (Wilcox et al., 1982, 1987; Kaufmann et al., 1987; Headley et al., 1996; Wallace et al., 1997, 1999), running (Fitzgerald, 1981; Floras & Wesche, 1992; Hara & Floras, 1992, 1995; Reukert et al., 1996), leg ergometry (Hannum & Kasch, 1981; Paulev et al., 1984; Somers et al., 1985, 1991; Coats et al., 1989; Floras et al., 1989; Pescatello et al., 1991; Southard & Hart, 1991; Boone et al., 1992; Cleroux et al., 1992; Landry et al., 1992; Franklin et al., 1993; Piepoli et al., 1993; Isea et al., 1994; Brownley et al., 1996; Halliwell et al., 1996a, b; Forjaz et al., 1998), and arm ergometry (MacDonald et al., 1999d). As summarised in chapter five, we recently examined the effects of the exercising muscle mass by comparing the PEH response to both leg and arm ergometry at the same relative intensity (MacDonald et al., 1999d). No differences in the magnitude of PEH were evident which led us to conclude that the amount of exercising muscle mass does not appear to influence the magnitude of the PEH observed.

Limited data suggest that PEH may occur after resistance exercise (Hill et al., 1989; Brown et al., 1994; Boer et al., 1995; MacDonald et al., 1999a). It should be noted that reductions in blood pressure in the seconds or brief minutes following resistance exercise can be attributed to the sudden perfusion of the previously occluded muscle mass and a transient pressure undershoot (MacDougall, 1985). These decrements should

not be confused with PEH, which is found in the prolonged minutes or hours after exercise. Although O'Connor et al. (1993) found elevations in both systolic and diastolic blood pressure after resistance exercise, others have found significant reductions. These reductions were found after whole body circuit training (Brown et al., 1994; Boer et al., 1995) and prolonged unilateral leg press exercise (MacDonald, 1999a). Studies directly comparing the haemodynamic responses to aerobic and resistance exercise indicate that there is no difference in the magnitude or duration of the observed hypotension between exercise modalities (Brown et al., 1994; MacDonald et al., 1999a).

In rodents, PEH has been found after spontaneous (Shyu & Thoren, 1986) and forced (Overton et al, 1988; Boone et al. 1996) running. Stimulation of the sciatic nerve (Yao et al 1981, 1982a, b; Shyu et al., 1984; Hoffman & Thoren, 1986; Kenney et al, 1991), the biceps femoris or the gastrocnemius muscles (Hoffman & Thoren, 1988; Hoffman et al., 1990) have also been demonstrated to evoke PSH.

2.3.3.2 Intensity Of The Exercise

In examining the effects of exercise intensity on PEH, the majority of studies have utilised submaximal cycle ergometry protocols at intensities that have ranged between 40 and 100% of maximal exercise capacity, as indicated by measurements of $\dot{V}O_2$, heart rate reserve, or predicted maximal heart rate (Hannum & Kasch, 1981; Paulev et al., 1984; Somers et al., 1985, 1991; Coats et al., 1989; Floras et al., 1989; Pescatello et al., 1991; Southard & Hart, 1991; Boone et al., 1992; Cleroux et al., 1992; Landry et al., 1992; Franklin et al., 1993; Piepoli et al., 1993, 1994; Isea et al., 1994; Brownley et al., 1996; Halliwell et al., 1996a, b; Forjaz et al., 1998). Treadmill exercise, at similar intensities, has also been documented to elicit PEH (Wilcox et al., 1982, 1987; Kaufmann

et al., 1987; Floras & Wesche, 1992; Hara & Floras, 1992, 1995; Headley et al., 1996; Reukert et al., 1996; Wallace et al., 1997, 1999). Direct comparisons of the effect of exercise intensity have, for the most part, found PEH to occur independent of exercise intensity. As documented in chapter three, we have found no difference in the magnitude of hypotension following 30 min of cycle ergometry at power outputs eliciting 50 and 75% $\dot{V}O_{2\,Peak}$ in normotensive volunteers (MacDonald et al., 1999b). Pescatello et al., (1991) found no difference in the magnitude of PEH observed following 30 min bouts of cycle ergometry at 40 and 70% of $\dot{V}O_{2\,Peak}$ in a hypertensive population. Using an even broader exercise spectrum, Forjaz et al. (1998) found similar hypotension following 45 min of exercise at intensities of 30, 50 and 80% of $\dot{V}O_{2Max}$. Using a resistance exercise model, Brown et al. (1994), compared three sets of five exercises at 40 and 70% of one repetition maximum (RM) and demonstrated significant PEH in a normotensive population with similar pressure decrements between trials. The decrease in blood pressure was comparable to the drop found after 25 min of cycle ergometry at 70% of $\dot{V}O_{2\,Peak}$. Only one study has reported differences in the hypotensive response to different exercise intensities. In that study, Piepoli et al. (1994) found decrements only after maximal cycle exercise (five min stages of 25 Watt increments) when compared to moderate (five min stages of 12.5 Watt increments) and minimal (constant 50 Watt) intensity exercise in normotensive volunteers. However, in that study, the subjects were described as "not regularly engaged in physically demanding jobs or sports". In this population, maximal exercise could more adversely affect the haemodynamic response to exercise than in the other studies. Significant thermoregulatory, SNS activity or

prostaglandin effects may occur after maximal exercise in such a population, which may differ from other forms of PEH.

In rats, PEH has been documented following treadmill exercise at 30 $m \cdot min^{-1}$ and 10% grade (Boone & Cory, 1996), 70% $\dot{V}O_{2Max}$, and spontaneous, self selected running (Shyu et al., 1986). Stimulation of the biceps femoris and gastrocnemius muscles at current intensities of 3 to 25 mA in the conscious rat has been found to induce PSH (Hoffman et al. 1986; Hoffman & Thoren, 1988). Additionally, sciatic nerve stimulation at intensities ranging from 4 to 25 times the minimum current intensity required to elicit a twitch has also been documented to cause PSH in conscious (Yao et al, 1981, 1982 a, b; Kenney et al., 1991; Hoffman & Thoren, 1986) and anaesthetised (Shyu et al, 1984) rats.

2.3.3.3 Duration Of The Exercise

PEH has been observed after as little as 10 min (Bennett et al., 1984; MacDonald et al, 1999c) and as long as 170 min (Seals et al., 1988) of exercise. However, the majority of studies have used endurance exercise lasting between 20 and 60 min (Fitzgerald, 1981; Hannum & Kasch, 1981; Paulev et al., 1984; Floras et al., 1989; Floras & Senn, 1991; Southard & Hart, 1991; Boone et al., 1992; Cleroux et al., 1992; Floras & Wesche, 1992; Hara & Floras, 1992, 1994, 1995; Landry et al., 1992; Isea et al., 1994; Brownley et al., 1996; Halliwell et al., 1996a, b; Reukert et al., 1996; Silva et al., 1997; West et al., 1998; MacDonald et al., 1999b, c, d, e, f). Inter-experimental comparisons are difficult across studies, since a variety of exercise intensities and blood pressure measurement techniques have been used.

In directly comparing the effect of exercise duration on PEH, Bennett et al. (1984) have suggested that, in hypertensive subjects, the magnitude of the pressure decrement

increases with a longer duration of exercise, but could not substantiate this in a normotensive population. However, in that study, blood pressure was measured during three min rest periods following successive 10 min exercise bouts. A brief hypotension immediately following exercise is often attributed to a pooling of blood in the vasodilated muscle beds. The mechanism for such decrements immediately following exercise may be considerably different from those involved in PEH. Forjaz et al. (1998) have found a greater decrement in both SBP and DBP and a longer duration of PEH in SBP following 45 min of exercise as compared to 25 min of exercise. Conversely, as documented in chapter four, we have recently found a similar magnitude of PEH following 10, 15, 30 and 45 min of exercise at 70% $\dot{V}O_{2\,Peak}$ (MacDonald et al., 1999c) in a normotensive and borderline hypertensive population. Although inconclusive, the results of our study also suggest that the duration of the hypotension may be influenced by the exercise duration.

We have found that as little as 15 min of resistance exercise (unilateral seated leg press at 65% 1RM) can evoke PEH (MacDonald et al., 1999a). Blood pressure reductions in that study were similar to those found after a short duration (~13 min) of bilateral cycle ergometry at 65% of $\dot{V}O_{2\,Peak}$.

Rodents have demonstrated PSH following stimulation of the sciatic nerve, gastrocnemius or biceps femoris muscles for durations lasting 30 to 60 min (Hoffmann & Thoren 1988, Hoffmann et al., 1990a, b). In spontaneously hypertensive rats, Overton et al. (1988) directly compared the effects of 20 and 40 min of treadmill running at 60-70% $\dot{V}O_{2\,Peak}$. In this population, those animals completing 40 min of exercise exhibited significantly greater decrements in blood pressure than those who ran for 20 min.

2.3.4 Duration Of The Response

The onset of hypotension following exercise has been found to occur within minutes after exercise (Boone et al., 1993; Piepoli et al., 1993, 1994) or at some time point between 30 min and one hour following exercise (e.g. Fitzgerald et al., 1981; Overton et al., 1988; Pescatello et al., 1991; Somers et al., 1991; Floras & Wesche, 1993; Franklin et al., 1993; MacDonald et al., 1999a). Most studies have measured blood pressure for only 1-2 hours following exercise (Wilcox et al 1982; Hagberg et al., 1987; Kaufman et al., 1987; Coats et al., 1989; Hara & Floras 1992, 1994, 1995; Brown et al., 1994; Headley et al., 1996 MacDonald et al., 1999a-f) and the majority of these have found a nadir in blood pressure during that time with a return or trend towards returning to baseline pressure at the cessation of measurement.

Practically, the PEH phenomenon will have clinical utility only if the relative hypotension is sustained for a significant duration and during activities of daily living. There have been a handful of studies that have examined the time course of PEH using ambulatory monitoring. We are aware of seven studies that have attempted to examine whether the hypotension is preserved during subsequent mild exercise or routine daily activities (Pescatello et al., 1991; Somers et al., 1991; Hara & Floras 1995; Brownley et al., 1996; Reuckert et al., 1996; MacDonald et al., 1999e; Wallace et al., 1999). Results from these studies are contradictory and may be confounded by the fact that, with the exception of one, post exercise activity was not controlled and that most investigators used intermittent auscultatory methods to determine blood pressure. Given the great differences in blood pressure between rest and activity and the influences of the breathing cycle and other cyclic waves on blood pressure, these auscultatory methods are prone to

sampling error and may provide inaccurate or inconsistent results. It should also be noted that in assessing these studies, some have failed to address the influences of diurnal variations in blood pressure by only comparing post-exercise blood pressure to a pre-exercise control value (Somers et al. 1991; Hara & Floras, 1995; Reukert et al., 1996). These studies failed to detect any long term reduction in blood pressure. Those comparing post exercise blood pressure to blood pressure following a control period of rest, in a free living environment, have found significant decrements in blood pressure for up to 12.7 hours in hypertensive individuals (Pescatello et al, 1991; Brownley et al., 1996; Wallace et al., 1999). No differences were found in normotensives. However, these studies may also be misleading, in that a bout of exercise may induce a more sedentary period post exercise under free living conditions. In the rodent model, it has been reported that exercise induces an opioid mediated drop in activity level, including reflexive activity (Hoffmann et al., 1990). Whether or not this occurs in humans is unknown. However, for those not involved in regular activity, a single session of moderate intensity exercise often induces a decrease in physical activity and energy expenditure in the hours post exercise (Kriemler et al., 1999).

As summarised in chapter six, we have recently completed a study in a controlled setting, using continuous, indwelling blood pressure and tracked the blood pressure changes during a standardised protocol of mild exercise and activities of daily living following both rest and a bout of cycle ergometry. Results indicated that decrements in SBP, DBP, and MAP remained statistically significant to the end of the 70 min monitoring period, with no trend towards returning to baseline values when preceded by prior exercise (MacDonald et al., 1999e). In our study, SBP averaged 16 mmHg, and as

much as 23 mmHg below control levels when preceded by a bout of exercise. It may be that activities of daily living, following exercise, potentiate the reductions in blood pressure. Studies in our laboratory, using a similar borderline hypertensive population, have found blood pressure returning to normal within the first hour after exercise when subjects remained sedentary (MacDonald et al., 1999c, d). A long duration, well controlled study needs to be completed to accurately assess the time course of PEH.

Hoffman and Thoren (1988) have indicated that blood pressure can remain significantly attenuated for 15 hours in the hypertensive rat following electrical stimulation of the biceps femoris muscle, with the nadir not occurring until six hours post stimulation. Others have found decrements in blood pressure persisting at the cessation of measurement between 20 min and six hours post exercise (Yao et al., 1982a, b; Hoffmann et al., 1990a; Chen et al., 1995; VanNess et al., 1996; Chandler & DiCarlo, 1997; Kulics et al., 1999).

The question remaining, in both the human and rodent models, is why do some studies report a rapid return to control levels, while others report a long duration hypotension? The possibility exists that pronounced, long duration blood pressure oscillations occur post exercise. Those studies that have observed blood pressure returning toward control levels, or terminated measurements within the first two hours following exercise, may not truly represent the longer term changes in blood pressure. Although an early study by Pescatello et al. (1991) does not report the blood pressure values tracked over the first hour post exercise, their subsequent measurements taken every 30 min for over 12 hours would suggest an oscillatory pattern of SBP.

2.3.5 Potential Mechanisms

Mean arterial blood pressure is a functional product of cardiac output and total peripheral resistance. With reference to these two basic components, the following is known:

2.3.5.1 Cardiac Output ($\dot{Q}c$)

Although no one has attempted to directly measure cardiac output during the hypotensive period after exercise, indirect measures have yielded contradictory results. $\dot{Q}c$ has been found to be increased through increased heart rate (Coats et al., 1989; Hara & Floras, 1992; Piepoli et al., 1993; Isea et al., 1994; Halliwell et al., 1996a; Headly et al., 1996; West et al., 1998), stroke volume (Kulics et al., 1999), or both (Floras et al., 1989; Cleroux et al., 1992). Conversely, others have reported $\dot{Q}c$ to be decreased (Hagberg et al., 1987; Floras & Wesche, 1992; Reukert et al., 1996). In all such instances the decrements were found to be due to reductions in stroke volume.

In humans, it is common to observe an increased heart rate during some or all of the hypotensive period (Coats et al., 1989; Hara & Floras, 1992; Piepoli et al., 1993; Isea et al., 1994; Halliwell et al., 1996a; Headly et al., 1996; West et al., 1998), whereas rodents often display decreased or unchanged heart rates (Hara & Floras, 1986, 1988; Overton et al., 1988; VanNess et al., 1996; Kulics et al., 1999). Of interest is that, with the exception of one study (Cleroux et al., 1992), changes in human cardiac output post exercise appear dependent on the initial state of hypertension. Those studies reporting indices of $\dot{Q}c$ in normotensives found increases in $\dot{Q}c$ during the post exercise hypotensive period, whereas hypertensives showed a decreased $\dot{Q}c$ (Hagberg et al., 1987; Coats et al., 1989; Floras & Wesche, 1992; Hara & Floras 1992; Halliwall et al.,

1996a; Headley et al., 1996; Reukert et al., 1996). These changes in $\dot{Q}c$ cannot be attributed to the exercise modality, duration or intensity since these studies have used a wide variety of protocols. In separate studies, using identical exercise protocols, Floras and colleagues demonstrated an increased $\dot{Q}c$ in normotensive and a decrease in $\dot{Q}c$ in hypertensive individuals (Floras & Wesche, 1992; Hara & Floras 1992).

2.3.5.2 Peripheral Resistance

In the vast majority of cases, indices of systemic and regional resistance are decreased below pre exercise values during the hypotensive period. A number of studies have found decreased peripheral resistance at sites other than those of the exercising muscle, suggesting that the reduction is a whole body phenomenon (Coats et al., 1989; Cleroux et al., 1992; Isea et al., 1994). However, Hagberg et al. (1987) found increases in total peripheral resistance in older hypertensives, suggesting that the mechanism(s) for PEH may differ between subject populations.

2.3.6 Mechanisms Affecting Cardiac Output And Peripheral Resistance

2.3.6.1 Thermoregulation

Cutaneous vasodilation is the primary mechanism for heat loss in humans. Given that exercise increases body temperature, it is possible that a re-distribution of blood to the periphery may be responsible for PEH. Franklin et al (1993) investigated this possibility by having normotensive subjects rest in a cool, neutral or warm environment after exercise. Hypotension was only evident in the group exposed to the warm environment. Although this may appear to support the hypothesis that cutaneous vasodilation mediates PEH, it is likely that this is a different phenomenon. Given the variable PEH response of normotensive individuals and the persistence of PEH for at

least one hour following mild exercise as brief as 13 min (MacDonald et al., 1999a), in which whole body heat dissipation would presumably have returned to normal, it is unlikely that cutaneous vasodilation is the primary mechanism responsible for PEH.

2.3.6.2 Blood Volume

During intense exercise, it is known that the increased blood pressure may drive plasma into the interstitial space, reducing blood volume. A reduction in blood volume would, in turn, cause decreased venous return to the heart. This would translate into a decreased stroke volume and therefore cardiac output. However, it would appear likely that reductions in plasma volume are not responsible for PEH. Although Hagberg et al. (1987) found slight post-exercise reductions in plasma volume in one group of hypertensives, the magnitude of the reduction was similar to that after a control period of rest. Other studies using measures of haematocrit and/or haemoglobin have found plasma volume to be unchanged after exercise and during periods of hypotension (Kaufmann et al., 1987; Cleroux et al., 1992b; MacDonald et al., 1999a, b, c, d). No studies have measured plasma volume during long duration PEH. However, it is generally accepted that due to the increased osmolarity following exercise, that plasma volume can expand to a greater extent than before exercise. Hypotension has been found to persist for greater than the one hour after moderate to intense exercise in which this increased plasma volume can occur (Cleroux et al., 1992; Headley et al., 1996).

2.3.6.3 Efferent Sympathetic Nerve Activity

A number of studies have examined the influence of sympathetic nerve activity on PEH. The use of microneurography has allowed researchers to directly measure sympathetic nerve activity. Measures of muscle sympathetic nerve activity (MSNA) as

an indication of vascular tone, have yielded contradictory results. Halliwell et al. (1996) has documented post exercise decrements in MSNA in a normotensive population, whereas others have found no changes (Floras et al., 1990; Hara & Floras, 1992). Floras and co-workers reported a reduced muscle sympathetic nerve activity following exercise in borderline hypertensives (Floras et al., 1989). It has been suggested that borderline hypertensive subjects (and presumably hypertensive subjects) exhibit higher than normal MSNA in the resting condition, and thus the observed hypotension was due to a transient suppression of augmented sympathetic outflow. Rodent data are no more conclusive. Following exercise, blood pressure and lumbar sympathetic nerve activity have been found to be reduced in spontaneously hypertensive rats (Kulics et al., 1999) and measures of splanchnic sympathetic nerve activity have been decreased in this same population (Yao et al., 1982a). On the other hand, in separate studies, Kenney et al. reported both unchanged renal and elevated lumbar sympathetic nerve activity (Kenney et al, 1993) and decreased renal sympathetic nerve activity (Kenney et al., 1991) after prolonged stimulation of the sciatic nerve in Dahl salt-sensitive rats.

Heart rate variability has also been used as an indication of the autonomic nervous system control. In both normotensive (Piepoli et al., 1993; Halliwell et al., 1996) and borderline hypertensive (MacDonald et al., 1999e, f) individuals, these indirect indices suggest that sympathetic outflow is increased over the same interval in which PEH is observed. This may be a reflexive response to partially offset the exercise induced hypotension.

Sympathetic nerve activity is manifested by release of norepinephrine from the sympathetic nerve endings. Norepinephrine binds to specific alpha receptors and, for the

most part, causes vasoconstriction. Measures of plasma norepinephrine levels as an indirect measure of "spill over" from sympathetic activity are inconsistent during PEH. Levels have been reported to be increased in normotensives (Landry et al., 1992), increased (Paulev et al., 1984) and unchanged (MacDonald et al., 1999f) in borderline hypertensives, and decreased in hypertensive individuals (Cleroux et al., 1992). Brownley et al. (1996) reported no change in urinary catecholamines after exercise in both normo and hypertensive individuals, with PEH only occurring in those with high blood pressure. Therefore, there is considerable disagreement as to whether changes in sympathetic activity might be responsible for PEH.

2.3.6.4 Afferent Nerve Activity

There is some indication that afferent nerve activity to cardiovascular control centres originating in certain peripheral sites may be involved in PEH/PSH. During exercise, unmyelinated group III afferents, termed "ergoreceptors", are activated (Mitchell, 1985). It is likely that any role in afferent induced hypotension would be in response to activation of the unmyelinated group III afferents. There are three such places that afferent activity that may influence PEH might originate:

2.3.6.4.1 Skeletal Muscle

Direct muscle stimulation of the biceps femoris or the gastrocnemius muscle of the rat has been found to elicit PEH (Hoffmann & Thoren, 1988; 1990a, b). However, PEH is abolished following stimulation of sciatic nerve anaesthetised animals. Kenney et al. (1991) have also observed PSH following stimulation of the medial end of the severed sciatic nerve. Although this evidence strongly supports skeletal muscle afferent involvement in PEH/PSH in rats, the potential mechanism of action is unknown.

2.3.6.4.2 Cardiac Muscle

Similar to skeletal muscle, cardiac afferents can be activated during exercise via increased heart rate, contractility and tension. In assessing their influence on PEH, Collins and DiCarlo (1993) examined the hypotensive response of rats to exercise during cardiac efferent (pericardial injection of scopolamine methyl bromide and propranolol) and combined efferent and afferent (pericardial injection of procainamide hydrochloride) blockade. The combined efferent and afferent blockade resulted in a significant attenuation of PEH as compared to control and cardiac efferent blockade, suggesting an influence of cardiac afferents on PEH.

2.3.6.4.3 Baroreceptors

During exercise, blood pressure is allowed to rise because of the withdrawal of baroreceptor mediated control. Baroreceptors are believed to "re-set" the cardiovascular control centre to a higher operating point during exercise (Guyton, 1980). It is unlikely that a downward set point established by the baroreceptors following exercise is responsible for PEH. Because of the mechanical compression of the blood vessels during heavy resistance exercise and the Valsalva manoeuvre which accompanies such exercise, blood pressure is increased to a much greater extent than during endurance exercise (MacDougall et al., 1994). Therefore, one could hypothesise that if baroreceptor re-setting were responsible for PEH, it would be expected that the decrements in blood pressure would be greater following resistance exercise. This is not the case. Both Brown et al. (1994) and MacDonald et al. (1999a) found similar decrements in blood pressure following resistance and endurance type exercise, whereas O'Connor et al., (1993) found decrements only after endurance exercise. However, the possibility exists

that the sensitivity of the baroreceptors is decreased with exercise, in that the reduced blood pressure is no longer an adequate stimulus to elicit the cardiovascular control centre excitation necessary to raise blood pressure. Using the lower body negative pressure method of baroreceptor sensitivity assessment, Bennett et al. (1984) found an increased baroreceptor sensitivity following exercise that elicited PEH. Similar increases in sensitivity have been observed using neck suction, indicating a baroreceptor mediated restraint of PEH (Halliwell et al., 1996a). Conversely, using the phenylephrine (Somers et al., 1985) and nitroprusside (Halliwell et al., 1996b) methods, baroreceptor sensitivity has been found to be depressed during at least some, but not all, periods of hypotension.

The most compelling evidence for baroreceptor mediated PEH comes from sinoaortic denervated rats. Chandler and DiCarlo (1997) found hypotension only after exercise in intact rats. No PEH was evident in sinoaortic denervated animals. Although with this method, it is not possible to deduce whether the "set-point" or the sensitivity of the baroreceptors is responsible for mediating PEH, these data would suggest that the sensitivity is altered.

2.3.6.5 Norepinephrine And Epinephrine

Sympathetic stimulation during exercise causes the adrenal medullae to release significant amounts of epinephrine and norepinephrine in proportion to the exercise intensity. As outlined above, the norepinephrine acts predominantly on peripheral alpha-receptors, causing vasoconstriction. The degree of vasoconstriction via alpha-receptor stimulation is dependent on the location within the body. The kidney, spleen and skin are known to be highly sensitive to alpha-receptor stimulation, whereas skeletal and cardiac muscle are not. In addition to the generalised vasoconstriction, both norepinephrine and

epinephrine also increase heart rate and contractility, and therefore cardiac output. The end product of this increase in peripheral resistance and cardiac output is an elevated arterial pressure. It has recently been shown that hypertensive individuals have increased basal sympathetic nerve activity (Grassi, 1998). Conversely, a decrease in circulating catecholamines after exercise could lead to PEH. However, as previously discussed, norepinephrine does not appear to contribute to PEH.

The circulating epinephrine released from the adrenal medullae binds to muscle β-receptors and has a moderate vasodilatory effect. Measures of circulating epinephrine indicate that levels are elevated (Landry et al., 1992) or unchanged (Wilcox et al., 1987; MacDonald et al., 1999f) during the hypotensive period. Our finding that PEH is largely independent of exercise intensity combined with the fact that it also persists during epinephrine infusion (Landry et al., 1992) and β-receptor blockade (Wilcox et al., 1987) suggests that any role of epinephrine in PEH is minimal.

2.3.6.6 Renin Angiotensin System

Renin is released from the kidneys during periods of low perfusion pressure. This enzyme causes the conversion of angiotensinogen to angiotensin I. In turn, angiotensin I is acted on by a converting enzyme to form angiotensin II which has powerful vasoconstriction and water and salt retention properties. However, during the hypotensive period after exercise, unchanged (Wilcox et al., 1982) and increased (Paulev et al., 1984; Peipoli et al., 1993) concentrations of circulating renin and increased angiotensin II concentrations have been found (Wilcox et al., 1982).

2.3.6.7 Antidiuretic Hormone (Vasopressin)

In addition to its primary role in controlling body water content, antidiuretic hormone can act as a vasoconstrictor of arterial smooth muscle. It is released from the pituitary gland during periods of low blood pressure or increased osmolarity/osmolality. Although long duration, exhaustive exercise can increase plasma osmolality, hypotension has been found during exercise in which insignificant changes in osmolality (Wilcox et al., 1982; Paulev et al., 1984) and increased (Wilcox et al., 1982) or unchanged (Paulev et al., 1984) levels of vasopressin are present. Wilcox et al. (1982) found no significant correlations between levels of antidiuretic hormone and the magnitude of PEH.

2.3.6.8 Atrial Natriuretic Peptide

Endurance type exercise results in increased right atrial filling. This increased volume and an increased heart rate can result in atrial natriuretic peptide release (Perrault et al., 1989). ANP has potent vasodilatory and sodium retention effects. The circulating half life of ANP is only 2-3 min, but it may still exert residual effects after it is cleared from the circulation (Davis 1989). The mechanism for this persistence is unknown. It would, however, appear that ANP is not responsible for the observed hypotension after exercise. Although Hara and Floras (1992) do not report ANP values during exercise, concentrations were significantly decreased from baseline values at one hour post exercise. We have recently examined the effects of resistance and endurance exercise on post exercise blood pressure and ANP release (MacDonald et al., 1999a). Although blood pressure was significantly reduced after exercise in both cases, no significant increases in circulating ANP concentrations were observed during or post exercise.

2.3.6.9 Potassium (K^+)

Potassium exerts a dilatory effect on vascular smooth muscle. It is released by tissue in response to low oxygen concentrations, and then is believed to diffuse back to the pre-capillary sphincters, the metarterioles and arterioles to have vasodilatory effects (Guyton & Hall, 1996). During exercise, plasma K^+ concentrations are known to increase significantly. This increase is proportional to the exercise intensity and directly reflects the activity of the muscle sodium-potassium pump (Medbo & Sejersted, 1990). However, the increase is short lived and often found to undershoot basal levels within minutes of recovery (Hallen et al., 1994; Medbo & Sejersted, 1990). Plasma concentrations of K^+ have been reported to be increased (Wilcox et al., 1987) or unchanged (Paulev et al., 1984; Hoffmann & Thoren, 1988) after exercise or stimulation induced hypotension. Because plasma K^+ concentration is proportional to exercise intensity, yet PEH does not appear to be intensity dependent (MacDonald et al., 1999b; Pescatello et al., 1991; Forajz et al., 1998) and because of its rapid clearance rate from plasma, it is unlikely to be involved in the PEH found long after exercise terminates.

2.3.6.10 Adenosine

Similar to K^+, yet much more potent, adenosine is released by active tissues during exercise and causes substantial vasodilation. Although no studies have measured adenosine concentrations during PEH, Sparks et al. (1980) suggested that, at least during flow restricted exercise, adenosine is responsible for an initial vasodilation during the minutes following exercise in dogs. Although the re-uptake of adenosine is also very rapid following exercise (Guyton & Hall, 1996), further work examining potential links between adenosine and the onset of PEH in humans is warranted.

2.3.6.11 Prostaglandins

Prostaglandins (PGs) are known to be liberated during exercise and cause vasodilation. A variety of prostaglandins are potent vasodilatory substances affecting mammalian arteries and veins and may act locally at the site of production (Ward, 1999). The lungs effectively metabolise PGEs, PGFs and, to a lesser extent, PGAs. Therefore continued production of these prostaglandins would be essential for the sustained regulation of blood pressure. Although most studies examining the role of prostaglandins have used an occluded blood flow model, Wilson and Kapoor (1993) measured increased $PGF_{1\alpha}$ and PGE_2 during wrist flexion exercise. Indomethacin diminished the prostaglandin release and decreased blood flow, suggesting that the released prostaglandins were responsible for vasodilatation and hyperaemia. In a flow restricted model, Morganroth et al. (1977) concluded that prostaglandins mediate a decrease in peripheral resistance for 35-40 min post exercise. No study has directly assessed the contribution of prostaglandins to PEH.

2.3.6.12 Reduced Vascular Sensitivity / Nitric Oxide

There is some evidence to suggest that an exercise induced decrease in vascular sensitivity may be responsible for PEH. Although Landry et al. (1992) was the first to suggest that variations in vascular sensitivity after exercise may be responsible for the observed drop in blood pressure in humans, much of the evidence is derived from other species. In excised aortic rings from the New Zealand white rabbit, reduced α-adrenergic mediated isometric tension was observed following exercise (Howard et al. 1992). In a separate study using rats, increased iliac blood flow was demonstrated to be mediated by decreased adrenergic receptor sensitivity (Patil et al., 1993). Although no PEH was

observed in that study and the reduced sensitivity could be related to numerous factors, inhibition of nitric oxide attenuated the decreased sensitivity after exercise, suggesting that nitric oxide may, at least partly be responsible for the decreased sensitivity post exercise. Using ganglionic blocked, intact, Dahl salt sensitive rats, Van Ness et al. (1996) found an exercise induced attenuation in blood pressure responsiveness to the α-adrenergic agonist phenylephrine that persisted until the cessation of measurement at 30 min post infusion. Reduced vascular responsiveness in humans requires further study, but remains an interesting possibility.

2.3.6.13 Opioids And / Or Serotonin

It has been hypothesised that exercise induced alterations in the opioid system may be a mechanism that centrally affects blood pressure (Boone et al., 1992; Hoffmann & Thoren, 1988). Although little is known about the mechanics of this system, it is speculated that opioids cause a decrease in sympathetic activity (Boone et al., 1992). Specifically, the ß-endorphins are known to increase during exercise, and are often attributed to the sensation of euphoria (Janal et al., 1984). Early work examining ß-endorphins and blood pressure found that infusion of ß-endorphins resulted in a prolonged drop in blood pressure. In the rat model, Hoffmann et al., (1990) elegantly showed that binding of ß-endorphin to the κ, and to a lesser extent the δ-receptors, was responsible for PEH. Human studies examining the contribution of the ß-endorphins to PEH have elicited contradictory results when blocking the opioid system with naloxone, an opioid receptor antagonist (Boone et al., 1992; Hara & Floras, 1992).

There has been some suggestion that a chemical link exists between the serotonergic system and the endorphins. Preliminary animal studies have found a

significant drop in blood pressure following infusion of ß-endorphins. However, no hypotension was found if ß-endorphins were infused into animals pre-treated with pCPA, a specific depletor of serotonin. Additionally, the hypotensive effect of the ß-endorphins was potentiated by fluoxetine, a specific serotonin re-uptake inhibitor (Lamaire et al., 1978). These results imply that ß-endorphins may be a stimulus for serotonin release which, in turn, or in conjunction with the ß-endorphins cause decreases in sympathetic outflow. The mechanism for this inhibition of sympathetic outflow is unknown. Serotonin has been found to increase during exercise. These increases have been detected in brain tissue of rats (Asmundsson et al., 1997) and in blood samples of humans (Steinberg et al., 1998).

Studies examining the role of serotonin in PSH, have been quite convincing in the rodent model. Blood pressure depression following stimulation has been found to be abolished with the infusion of pCPA (Yao et al., 1982; Hoffman & Thoren, 1988) and augmented following treatment with the serotonin precursor 5-HTP or the serotonin re-uptake inhibitor zimelidine (Yao et al., 1982).

2.4 SUMMARY

An understanding of the factors that cause and affect PEH may lead to a better understanding of the causes of hypertension, a condition that knowingly affects more than one in ten individuals. In addition, it is possible that the phenomenon may be exploited to provide a practical intervention in the management of this disease. PEH has been well documented to occur in the laboratory. Although some studies suggest that the hypotensive effect occurs during periods of free living, a well controlled study has yet to determine the extent to which lowered blood pressure persists beyond 70 min post

exercise. Further work needs to examine the time course of PEH under normal living conditions. It is generally accepted that borderline and hypertensive individuals will experience a greater drop in blood pressure post exercise than those without high blood pressure.

It is evident that, although PEH occurs in both humans and rodents, the mechanism(s) of action may not be consistent between species. In general, the magnitude of PEH does not appear to be correlated with the exercise intensity, duration or the amount of exercising muscle mass. PEH has been found after a variety of exercise stimuli including both endurance and resistance exercise. However, the possibility exists that the duration of the PEH may be influenced by any of these factors and warrants further study.

A review of the available literature has failed to elucidate any definitive mechanism(s) underlying PEH. Although the decreased blood pressure following exercise has mainly been found to be due to a decreased vascular resistance, the underlying cause for this decreased resistance has yet to be determined.

It is likely that PEH is not the result of thermoregulation or changes in blood volume. Although some data have suggested decreases in efferent nerve activity following exercise, contradictory reports across both humans and rodents are inconclusive. Reports of afferent nerve activity have implied their role in contributing to PEH, however the site of action (baroreceptors, hormones or efferent nerve activity) needs to be further investigated.

Significant evidence in the rat model has suggested that central serotonin levels may influence PEH, but our recent study in humans (chapter seven) indicates that central serotonin is not responsible for PEH in our borderline hypertensive population.

It also appears unlikely that circulating hormones or other local factors are responsible for PEH *per se*. Measured concentrations of potential vasodilators such as epinephrine, adenosine, potassium and atrial natriuretic peptide have been reported to be increased or unchanged after exercise induced hypotension. Vasoconstricting substances such as renin, angiotensin II and antidiuretic hormone have been found to be increased, decreased or unchanged after exercise that elicits PEH. There are reports of PEH persisting for up to 17 hours after exercise. At this time, each of these substances could be presumed to have returned to normal levels. The possibility does exist that any of these substances may be responsible for alterations in vascular sensitivity and therefore, indirectly mediate PEH. The role of nitric oxide in this possible change in vascular responsiveness has yet to be determined, but does appear encouraging from animal work.

The contradictory results found between mechanisms such as muscle sympathetic nerve activity, the opioid system as well as the large variations observed between the existence, magnitude and response of PEH, suggest that it is a phenomenon which is not controlled by a single factor. A complex matrix of blood pressure regulating factors including both central and peripheral mechanisms are likely responsible for PEH and require further investigation.

2.5 PURPOSE

The purpose of this thesis was to explore some of the potential causes and mechanisms of PEH. The format of this thesis is a compilation of experiments

previously published or submitted for publication, arranged as chapters. At the time of study, little was known regarding the type of exercise stimuli needed to elicit PEH. Chapters three through five summarise the investigations of the effects of exercise intensity, duration and the contribution of central versus peripheral factors through the influence of exercising muscle mass on PEH. These studies documented that the exercise needed to elicit PEH was of sufficiently low intensity and duration that it could be readily attainable by those often diagnosed with hypertension, namely the elderly and obese. It was also documented in chapter five that the blood pressure decline was of similar magnitude regardless of the exercising muscle mass. This would suggest a central modulation of PEH. In chapter six, an investigation of possible application of PEH to assist in the management of hypertension is presented. Here it is demonstrated that PEH persists and may, in fact be augmented, through mild exercise and activities of daily living. An investigation of some of the potential mechanisms for PEH is summarised in chapter seven. Although rodent work had established strong evidence supporting a link between the central serotonergic system and post exercise hypotension, our results indicate that no such link exists in humans. A brief summary of the results and a discussion of future directions are presented in chapter eight.

CHAPTER 3

The Effects Of Exercise Intensity On Post Exercise Hypotension

THE EFFECTS OF EXERCISE INTENSITY ON POST EXERCISE HYPOTENSION

MacDonald, J.R., J.D. MacDougall, C.D. Hogben. The effects of exercise intensity on post exercise hypotension. *Journal of Human Hypertension* 13:527-531, 1999.

Jay R. MacDonald's Contribution:
a) study design
b) data collection
c) data analysis
d) manuscript preparation

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ORIGINAL ARTICLE

The effects of exercise intensity on post exercise hypotension

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Ten normotensive, recreationally active participants aged 35.0 ± 16.3 years, volunteered to participate in the study. Average baseline blood pressure (BP) was 132/75 mm Hg for systolic (SBP) and diastolic (DBP) pressure respectively. On two separate days, participants underwent testing in a randomised, repeated measures fashion such that they performed 30-min bouts of cycle ergometry at a power output which elicited 50 or 75% of $\dot{V}O_{2\,Peak}$. Blood pressure was monitored continuously throughout the session by the Finapres method with 2-min windows recorded at rest, 5, 10, 15, 30, 45 and 60 min post exercise.

SBP was similar between the two trials and became hypotensive at 5 through 15 min post exercise. The largest decrement (8 mm Hg) in SBP occurred 5 min post exercise. DBP was also unaffected by the intensity of exercise and was lower than before exercise at 5 and 15 through 45 min post exercise. Similarly, mean arterial pressure (MAP) showed significant decrements at 5 and 15 through 45 min post exercise irrespective of exercise intensity.

Heart rate was greater during the 75% intensity than during the 50% intensity trial. Pre-exercise values were re-established by 45 min post exercise. $\dot{V}O_2$ remained significantly elevated above pre-exercise values in both trials until 15 min post exercise. Haematocrit increased significantly during both exercise bouts but returned to pre-exercise values by 10 min post exercise.

This study indicates that cycle ergometry at 50 and 75% of $\dot{V}O_{2\,Peak}$ elicit similar reductions in post exercise BP. Therefore bouts of mild to moderate intensity exercise may be beneficial in the control of hypertension.

Keywords: Finapres; blood pressure; cycle ergometry; haematocrit; endurance exercise

Introduction

It is generally accepted that endurance exercise training can, over time, decrease resting blood pressure (BP) in hypertensive and borderline hypertensive individuals.[1] However, since Fitzgerald[2] suggested that an acute bout of exercise may also aid in transiently decreasing BP during the post exercise period, few researchers have attempted to determine the characteristics of an exercise bout that is necessary to elicit this post exercise hypotension (PEH).

In examining the effects of exercise intensity on PEH, the majority of studies have utilised submaximal cycle ergometry protocols at intensities which have ranged between 40 and 100% of maximal exercise, as indicated by measurements of $\dot{V}O_2$, heart rate reserve or predicted maximal heart rate.[3-10] Treadmill exercise at similar intensities has also been shown to elicit PEH. Direct comparisons of the effect of exercise intensity on PEH have been limited to 40 and 70% of maximal exercise. In a hypertensive population, Pescatello *et al*,[6] found no difference in the magnitude of PEH observed following 30-min bouts of cycle ergometry at these intensities. This PEH was absent their normotensive population. Brown *et al*,[11] using in a resistance exercise protocol of three sets of five exercises at 40 and 70% of one repetition maximums (1RM), demonstrated significant PEH in a normotensive population with similar pressure decrements between trials. The decrease in BP was comparable to the drop shown after 25 min of cycle ergometry at 70% of $\dot{V}O_{2\,Peak}$. Piepoli *et al*[5] found decrements only after maximal cycle exercise (5 min stages of 25 Watt increments) as compared to moderate (5 min stages of 12.5 Watt increments) and minimal (constant 50 Watt) intensity exercise in normotensive volunteers. Unfortunately, these studies used intermittent auscultatory BP measurement techniques, and in some cases, more than one technique was used over the duration of the study.[6] Given the presence of respiratory waves, Mayer waves and inter-experimenter variability, the accuracy of these auscultatory measurements may be questionable. The above studies are not conclusive in determining both the existence of PEH in a normotensive population and the possible effects of exercise intensity. This may be due to the auscultatory measurement techniques used.

Using intra-arterial BP monitoring, we have recently documented similar pressure decrements after each of 15 min of unilateral seated leg press at 65% 1RM and bilateral cycle ergometry at 65% of $\dot{V}O_{2\,Peak}$[12] in a normotensive population. Therefore, it was felt that before further mechanistic studies are undertaken, it is important to accurately describe the exercise conditions that elicit PEH using continuous monitoring techniques. The purpose of this

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study was, therefore, to determine the effects of different exercise intensities on the magnitude of the post exercise hypotensive response using a continuous BP monitoring technique in a normotensive population.

Subjects and methods

Finapres validation

During this study, the Finapres (Ohmeda, Louisville CO, USA) BP monitor was used. Although numerous researchers (eg, Parati *et al*[13] and Van Egmond *et al*[14]) have previously validated the Finapres, we also performed comparisons with simultaneous intra-arterial measurements. In our experience, resting Finapres measurements slightly but consistently under-estimated intra-arterial recordings (<10%) but tracked the pressure waveform remarkably well. This under-estimation was more pronounced in the diastolic readings. This held true during any activity of mild to moderate intensity in which the upper body was static (ie, static and dynamic leg press and Valsalva manoeuvre). During transition to dynamic endurance exercise (ie, rest to cycling) the Finapres tracings were erratic and did not accurately reflect intra-arterial values. Similarly, steady state, dynamic cycling produced values which sporadically misrepresented intra-arterial recordings (MacDonald JR and MacDougall JD, unpublished observations). However, for rest and seated recovery from cycle ergometry, the Finapres was found to provide an accurate representation of BP trends. Since the exercise BP measurements were not considered representative of the true pressures achieved during cycle ergometry they are not reported here.

Preliminary testing

Prior to the study, subjects' maximal oxygen uptake ($\dot{V}O_{2\,Peak}$) was determined using an incremental cycle ergometry test as previously reported.[12] All subjects also provided typical 4-day diet records (3 weekday, 1 weekend day). From these, average daily caloric intake was estimated and habitual diets were designed to be ingested on the day previous to testing and the testing day. These diets approximated each subject's average caloric content and restricted the consumption of stimulants and depressants known to affect BP (eg, caffeine and alcohol). Additionally, on those days, activity was minimal and consistent between trials.

On five separate days, participants were required to undergo resting Finapres BP measurement after a seated period of 20–30 min. The five systolic and five diastolic BPs were averaged and 1 standard deviation (s.d.) was calculated. If, during one of the experimental trials, initial resting pressure (either systolic or diastolic) was not within 1 s.d. of the subject's pre-trial average, the test was terminated and rescheduled for another day.

Subjects

Ten normotensive, recreationally active participants (4 female, 6 male) aged 35.0 ± 16.3 (mean±s.d.) years, with a mean height of 175.0 ± 11.7 cm and a mean weight of 76.4 ± 14.6 kg volunteered to participate in the study. Average baseline BP was 132(±17)/75(±14) mm Hg for systolic and diastolic pressure respectively. The McMaster University Human Ethics Committee approved this study, and subjects were advised of any risks associated with the protocol and provided written informed consent.

Methods

Participants completed a sub-maximal cycling protocol on two separate days. On each occasion, after a 4 h fast, the subjects reported to the laboratory and remained quietly seated for ~30 min. They then underwent resting Finapres BP measurements. The Finapres transducer was supported at mid-sternal level and coupled to an on-line data acquisition package (Windaq/200, DataQ Instruments Inc, Akron, OH, USA) sampling at a frequency of 300 Hz. Calibration of the Finapres was completed using an internal calibration sequence as well as a mercury manometer. The transducer was calibrated to show a linear response between 0 and 300 mm Hg. Testing was conducted in a randomised, repeated measures design such that each subject performed 30-min bouts of cycle ergometry at power outputs which elicited 50 and 75% of $\dot{V}O_{2\,Peak}$, in a randomised order. Prior to and following exercise, subjects remained quietly seated in a thermo-neutral environment (23°C, 50% humidity).

Finapres BP was monitored continuously throughout the session with 2-min windows recorded at rest, 5, 10, 15, 30, 45 and 60 min post exercise for subsequent analysis. During the 75% intensity trial, finger tip blood samples were taken at rest, immediately after 30 min of exercise and subsequent to the 10, 30 and 60 min post exercise pressure monitoring time point for the determination of haematocrit (Hct).

Oxygen consumption ($\dot{V}O_2$) was monitored periodically during exercise and during recovery at the time points listed above.

Analysis

Blood pressure waveforms were analysed using the Windaq data analysis program (DataQ Instruments Inc). Systolic (SBP) and diastolic BP (DBP) were calculated as the highest point and lowest point prior to the last inflection point in the waveform, respectively. The quotient of the integrated pressure and the duration of the time interval determined mean arterial pressure (MAP).

All BP and oxygen consumption variables were assessed using single, two-factor repeated measures analyses of variance (ANOVA) with trial and time of measurement as the repeated measures. Haematocrit was assessed using a single factor, repeated measures ANOVA with time of measurement as the repeated measure. The Tukey Honestly Significant

Difference (HSD) method was used to identify the location of any significant differences. A probability level of $P \leq 0.05$ was considered statistically significant. All values are expressed as mean ± standard deviation.

Results

As shown in Figure 1, SBP showed a significant main effect for time of measurement [$(F(6,54) = 2.84$, $P = 0.02$], with values at 5 through 15 min post exercise being significantly lower than baseline values. SBP was lowest 5 min post exercise (124 ± 15 mm Hg) and then gradually increased towards baseline values (132 ± 17 mm Hg) during the remaining 55 min. The intensity of exercise had no effect on the magnitude of this response.

The intensity of exercise also showed no significant effect on DBP. Across the two intensities however, DBP was significantly [$(F(6,54) = 2.76$, $P = 0.02$] reduced at 5 min post exercise and then again between 15 and 45 min post exercise. The largest decrement of 5 mm Hg was found 30 min after the cessation of exercise (75 ± 14 *vs* 70 ± 13 mm Hg). MAP (Table 1) was also not affected by the exercise intensity. However, across intensities, MAP showed significant decrements [$(F(6,54) = 3.41$, $P < 0.01$] at 5 min post exercise and then again between 15 and 45 min post exercise. The nadir of the MAP response occurred 15 min after exercise and was 6 mm Hg (93 ± 15 *vs* 87 ± 15 mm Hg).

As expected, there was a greater overall heart rate [$(F(1,9) = 32.57$, $P < 0.01$] during the 75% intensity trial above that achieved during the 50% intensity trial. Additionally, across both exercise intensities [$(F(8,72) = 146.92$, $P < 0.01$], heart rate was elevated to ~86 (±14) beats per min at 5 min post exercise from the resting value of ~71 (±7) beats per min after which, it steadily declined. Baseline values were re-established by 45 min post exercise. *Post hoc* analysis also identified a significant interaction [$(F(8,72) = 16.22$, $P < 0.01$], in that at all time points following exercise, heart rate was increased during the 75% intensity trial above that found during the 50% intensity trial (Table 2). $\dot{V}O_2$ remained significantly elevated [$(F(8,72) = 136.92$, $P < 0.01$] above resting values across both trials at 5 and 10 min post exercise and had returned to normal by 15 min after exercise.

Measures of haematocrit (Table 3) during the 75% intensity trial ($n = 9$) revealed an increase [$(F(3,32) = 8.37$, $P < 0.01$] above resting values of 45.2% (±3.6) to a high of 47.1 (±3.6) after 30 min of exercise. Pre-exercise haematocrit values were re-established by 10 min post exercise.

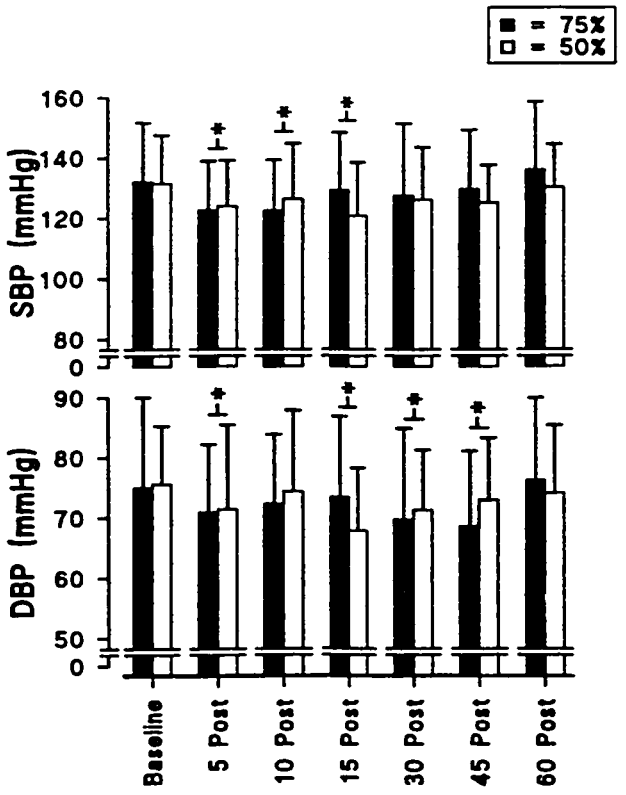

Figure 1 The combined effects of exercise intensity at 50 and 75% of $\dot{V}O_{2\,peak}$ on post exercise BP. *Indicates significant difference from baseline.

Discussion

This study has documented that both mild (50% $\dot{V}O_{2\,Peak}$) and moderate (70% $\dot{V}O_{2\,Peak}$) intensity exercise elicit similar magnitudes of PEH in a normotensive population. Auscultatory techniques have elicited mixed results of PEH in a normotensive population.[6,8,11] This may be due to the inability of those methods to detect the oscillatory nature of BP. As we have previously shown using direct measurement of BP,[12] this study confirms the existence of PEH in a normotensive population, although the decrements found here (~8/5 mm Hg) are of lesser magnitude than those often seen with a hypertensive population.[15] This may be interpreted as suggesting that hypertensive individuals may receive a greater benefit from an acute bout exercise than the subjects in the present study.

Additionally, we have demonstrated that otherwise identical bouts of cycle ergometry at power outputs eliciting 50 and 75% of $\dot{V}O_{2\,Peak}$ evoke similar magnitudes of PEH. Although Pescatello *et al.*[6] found similar results for hypertensives exercising at 40 and 70% of maximal endurance exercise, the results presented here are contradictory to previous reports found in normotensives. These results lend support to earlier work from our laboratory indicating similar pressure decrements after 15 min of unilateral leg press resistance exercise at 65% 1RM and cycle ergometry at 65% of $\dot{V}O_{2\,Peak}$[12] and the results of Brown *et al.*[11] showing similar BP responses after 40 and 70% of maximal resistance exercise. Both of these studies involved normotensive volunteers.

It is apparent that there is a complex matrix of interactions that determine the occurrence of PEH. Although both SBP and DBP were reduced in the present study, the duration of the drop was longer DBP. It is generally found that SBP demonstrates the

Table 1 The effects of exercise intensity at 50 and 75% $\dot{V}O_{2\,peak}$ on post exercise mean arterial pressure

MAP (mm Hg)	*Baseline*	*5 Post**	*10 Post*	*15 Post**	*30 Post**	*45 Post**	*60 Post*
75%	92(±18)	86(±13)	88(±13)	89(±16)	86(±17)	85(±15)	92(±16)
50%	93(±12)	89(±15)	91(±15)	85(±14)	89(±13)	89(±12)	92(±13)

*Indicates pooled data is significantly different from baseline.

Table 2 The effects of exercise intensity at 50 and 75% $\dot{V}O_{2\,peak}$ on post exercise heart rate

Heart rate (bpm)	*Baseline*	*During 15**	*During 30**	*5 Post**	*10 Post**	*15 Post**	*30 Post**	*45 Post**	*60 Post*
75%†	70(±8)	147(±20)‡	152(±20)‡	93(±12)‡	88(±8)‡	86(±9)‡	82(±9)‡	79(±10)‡	73(±10)‡
50%	72(±6)	121(±10)	122(±13)	80(±11)	77(±10)	75(±8)	70(±7)	68(±7)	68(±4)

*Indicates pooled data is significantly different from baseline, †indicates a main effect for trial, ‡indicates data is significantly different from the same time point during the 50% $\dot{V}O_{2\,peak}$ trial.

Table 3 The effects of exercise at 75% $\dot{V}O_{2\,peak}$ on post exercise haematocrit

Haematocrit (%)	*Baseline*	*During 30**	*10 Post**	*30 Post*	*60 Post*
75%	45.2(±3.6)	47.1(±3.6)	46.0(±3.9)	44.9(±4.0)	45.6(±3.8)

*Indicates data is significantly elevated from baseline.

larger decrement as well as the longest duration[6] in a hypertensive population. However, some evidence has suggested that in the normotensive population, the DBP response may be more prolonged[16] as found here.

In the present study the pattern of hypotension is such that BP drops shortly after the cessation of exercise and either trends back towards baseline values over the rest of the hour (SBP) or generally remains depressed until a return to baseline at the end of the hour (DBP and MAP). This is in contrast to data from our laboratory for a normotensive population which displayed a gradual drop in SBP and MAP from the cessation of exercise until 30 min post exercise and then a gradual return towards baseline[12] (MacDonald and MacDougall, unpublished observations).

Although it was not the purpose of the present study to examine the causal mechanisms of PEH, based on our data some possibilities may be dismissed. Since haematocrit had returned to resting levels by 10 min post exercise and the hypotension persisted until 45 min post exercise, a shift of plasma volume causing a decreased total blood volume and subsequent drop in pressure does not appear to be responsible for the decline in BP. We have also examined the effect of maintaining a static body position on BP for the 60 min post exercise period. Finapres and intra-arterial measurements indicated that 75 min of resting in a seated position, on its own (ie, without being preceded by exercise) did not result in a decline of BP[12] (MacDonald JR and MacDougall JD, unpublished observation).

Skin and rectal temperatures were not measured in this study, but the moderate intensity and short duration of exercise would suggest that thermoregulatory processes are not the cause of the PEH. Franklin *et al*[5] has demonstrated that 30 min of cycle ergometry at 70% $\dot{V}O_{2\,Peak}$ in a thermo-neutral environment (as in the present study), elicited a skin temperature which was actually decreased shortly after exercise, arguing against cutaneous vasodilation as the cause of PEH in the present study.

Although more work is warranted to accurately describe the characteristics and mechanisms of PEH, it seems plausible that acute exercise may aid in the non-pharmacological control of hypertension. It appears that the intensity of exercise need not be greater than 50% $\dot{V}O_{2\,Peak}$. This intensity could be equated to a brisk walk, which is a readily attainable exercise for most hypertensive individuals. Recent evidence has suggested that PEH may persist for up to 17 h[16] (Dr J Hagberg, personal communication). If this duration of response is achieved with the exercise indicated here, a series of moderate exercise sessions at a mild intensity (50% $\dot{V}O_{2\,Peak}$) spaced throughout the waking hours may be an effective addition to the treatment of hypertension.

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CHAPTER 4

The Effects Of Exercise Duration On Post Exercise Hypotension

THE EFFECTS OF EXERCISE DURATION ON POST EXERCISE HYPOTENSION

MacDonald, J.R., J.D. MacDougall, C.D. Hogben. The effects of exercise duration on post exercise hypotension. In press, *Journal of Human Hypertension*, 2000.

Jay R. MacDonald's Contribution:
a) study design
b) data collection
c) data analysis
d) manuscript preparation

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ABSTRACT

Study 1.

Thirteen normotensive participants with average baseline blood pressure of 126 / 71 mmHg participated in the study. Participants performed bouts of cycle ergometry for 15, 30 and 45 min at 70% $\dot{V}O_{2\,Peak}$. Blood pressure was monitored by the Finapres method with 2 min windows recorded at rest, 5, 10, 15, 30, 45 and 60 min post exercise. Following exercise, SBP was similar between the three trials and was reduced from pre-exercise values at 5 through 60 min of measurement. DBP was also unaffected by the duration of exercise and was lower than before exercise at 30 through 45 min post exercise.

Study 2.

Eight borderline hypertensive participants with average baseline blood pressure of 133 / 79 mmHg participated in the study. Subjects performed bouts of cycle ergometry for 10 and 30 min at 70% $\dot{V}O_{2\,Peak}$. Following exercise, blood pressure was monitored as in study 1. SBP was similar between both trials and was reduced from baseline at 5 through 60 min post exercise. The largest decrement of SBP was 14 mmHg and occurred 15 min post exercise. DBP was also unaffected by the duration of exercise and was lower than pre-exercise levels at 5 min and again at 15 through 45 min post exercise. MAP also showed significant decrements throughout the entire 1 hr post exercise period by a maximum of 9 mmHg at 15 min post exercise, irrespective of exercise duration. We conclude that moderately intense exercise may be as brief as 10 min in duration in order to elicit a decrease in resting blood pressure and may have potential benefits as a non-pharmacological aid to hypertension.

Keywords: blood pressure, cycle ergometry, haematocrit, endurance exercise, exercise duration, hypotension

INTRODUCTION

Chronic endurance exercise has been shown to result in a decrement in resting blood pressure [1,2]. In addition, an acute bout of exercise can cause a transient lowering of blood pressure in the period following exercise. This was first documented by Fitzgerald [3] who anecdotally reported the temporary decrease of his hypertension following acute sessions of jogging. Although this phenomenon has received little attention, more recent investigations have focused on potential mechanisms [4,13]. Unfortunately, the characteristics of the post exercise hypotension (PEH) and the exercise needed to elicit it have not been well outlined.

In examining the effects of exercise duration, Bennett et al. [4] have suggested that, in hypertensive subjects, the magnitude of the pressure decrement increases with an increased duration of exercise, but could not substantiate this in a normotensive population. In that study, however, blood pressure was measured during 3 min rest periods following successive 10 min exercise bouts. A brief hypotension immediately following exercise is often attributed to a pooling of blood in the vasodilated muscle beds. The mechanism of such decrements immediately following exercise may be considerably different from those involved in the PEH, which has been documented to last for 1 hour or more [i.e. 5].

We have recently shown significant reductions in post exercise blood pressure following as little as ~13 min of cycle ergometry at 65% of $\dot{V}O_{2\ Peak}$ [5], while others have observed PEH following exercise durations lasting between 20 and 170 min [e.g. 6,7,8,9]. However, inter-experimental comparisons are difficult, since a variety of exercise intensities and blood pressure measurement techniques have been used.

Although little is known about the causative mechanisms for PEH, it seems plausible that, in addition to the chronic effects of exercise, an acute bout may also have the potential to serve as a non-pharmacological intervention in the control of hypertension. Before further mechanistic studies are undertaken, it is important to accurately describe the exercise conditions that elicit PEH. The purpose of these studies was, therefore, to determine the effects of different exercise durations on the magnitude of the post exercise hypotensive response.

METHODS

Data presented in this paper was collected with the Finapres (Ohmeda, Louisville, CO) blood pressure monitor. Others and we have previously validated this method for baseline and post exercise measurements. [10, 11, 12] In our hands, steady state, dynamic cycling produced Finapres values that sporadically misrepresented intra-arterial recordings [MacDonald, J.R. & MacDougall, J.D., unpublished observations]. Since the Finapres values recorded during exercise were not considered to represent true blood pressures, they are not reported here.

Preliminary Testing

Before each study, subjects' maximal oxygen uptake ($\dot{V}O_{2\,Peak}$) was determined using an open circuit spirometry, incremental cycle ergometry test as previously described [5]. All subjects also provided typical 4 day diet records (3 weekday, 1 weekend day). From these, average daily caloric intake was estimated and habitual diets were designed to be ingested on the day before testing and on the testing day. These diets approximated each subject's average caloric content and restricted the consumption of

stimulants and depressants known to affect blood pressure (e.g. caffeine and alcohol). Additionally, on those days, physical activity was minimal and consistent between trials.

On 5 separate days, participants were required to undergo resting Finapres blood pressure measurement after a seated period of 20 - 30 min. The systolic and diastolic blood pressure values from each day were averaged and 1 standard deviation was calculated. If, during one of the experimental trials, initial resting pressure (either systolic or diastolic) was not within 1 standard deviation of this pre trial average, the test was terminated and rescheduled for another day. This occurred during three trials.

Study #1 - The Effects Of 15, 30 And 45 Minutes Of Exercise

Subjects

Thirteen normotensive, recreationally active males aged 22±0.8 (mean±SD) years, with a mean height of 179±8 cm and a mean weight of 79±14 kg volunteered to participate in the study. This study was approved by the McMaster University Human Ethics Committee, and subjects were advised of the risks associated with the protocol before providing written informed consent.

Methods

Participants completed a sub-maximal cycling protocol on 3 separate days. On each occasion, after a 4 h fast, the subjects reported to the laboratory and remained quietly seated for 30 min. They then underwent resting Finapres blood pressure measurements verified by auscultation. The Finapres transducer was placed at mid-sternal level and coupled to an on-line data acquisition package (Windaq/200, DataQ Instruments Inc., Akron, OH) sampling at a frequency of 300 Hz. Calibration of the Finapres was completed using an internal calibration sequence as well as a mercury

manometer. The transducer was calibrated to show a linear response between 0 and 300 mmHg. Testing was completed in a randomised, repeated measures fashion such that each subject performed bouts of 15, 30 and 45 min of cycle ergometry at a power output which elicited 70% $\dot{V}O_{2\ Peak}$.

Finapres blood pressure was monitored continuously throughout the session with 2 min windows recorded at rest, 5, 10, 15, 30, 45 and 60 min post exercise for subsequent analysis. During the 45 min of cycle ergometry trial, finger tip blood samples were taken at rest, after each 15 min of exercise and after each post exercise pressure monitoring time point for the determination of haematocrit (Hct).

Oxygen consumption ($\dot{V}O_2$) was monitored periodically during exercise and during recovery at the time points listed above.

Study #2 - The Effects Of 10 And 30 Minutes Of Exercise

Given the somewhat unexpected findings in study 1 that 15 min of exercise resulted in similar post exercise hypotension as that following 45 min of exercise, we decided to investigate the effects of 10 min of exercise on recovery blood pressure. In addition, because of our interest in the potential application of such exercise as an aid for controlling hypertension, we decided to recruit a more hypertensive group of subjects.

Subjects

Eight borderline hypertensive, recreationally active participants (2 female, 6 male) aged 23±4 (mean±SD) years, with a mean height of 177±12 cm and a mean weight of 79±4 kg volunteered to participate in the study. The McMaster University Human Ethics Committee approved this study and subjects were advised of any risks associated with the protocol and provided written informed consent.

Methods

Methods were as above in study 1. Testing was completed in a randomised, repeated measures design such that each subject performed bouts of 10 and 30 min of cycle ergometry at a power output which elicited 70% $\dot{V}O_{2\ Peak}$. All blood pressure, heart rate and $\dot{V}O_2$ measures were completed as in study 1.

Analysis

For both studies, blood pressure waveforms were analysed using the Windaq data analysis program (DataQ Instruments Inc., Akron, OH). SBP and DBP were calculated as the highest point in the waveform and the lowest point in the waveform before the last inflection point, respectively. Mean arterial pressure (MAP) was determined by the quotient of the integrated pressure and the duration of the time interval.

All blood pressure and oxygen consumption variables were assessed using single, 2 factor repeated measures ANOVAs with trial and time of measurement as the repeated measures. Haematocrit was assessed using a single factor, repeated measures ANOVA with time of measurement as the repeated measure. The Tukey Honestly Significant Difference (HSD) method was used to identify the location of any significant differences. A probability level of $p<0.05$ was considered statistically significant. All values are expressed as mean ± standard deviation.

RESULTS

Study # 1 - the effects of 15, 30 and 45 minutes of exercise

The effects of exercise on post exercise blood pressure are illustrated in Fig. 1. SBP was significantly [$F(6,72)=9.31$, $P<0.01$] reduced from pre-exercise values between 5 and 60 min post exercise, inclusive. This was independent of exercise duration. The

nadir of the response occurred at 45 min post exercise and was 12 mmHg below pre-exercise values (126.0±13.4 vs. 114.3±13.5). Although the duration of exercise had no statistical effect on the magnitude of this response [$F(12,144)=1.36$, $P>0.05$], SBP appeared to be returning to normal by the end of the 1h post exercise period after the 15 and 30 min of exercise trials (Figure 1). However, at the end of monitoring following 45 min of exercise, SBP was declining.

************Figure 1 About Here***********

DBP was significantly [$F(6,72)=6.04$, $P<0.01$] reduced between 30 and 45 min post exercise with the largest decrement of 4.6 mmHg 45 min after the cessation of exercise (71±9 vs. 66±9). This was independent of exercise duration.

MAP showed significant [$F(6,72)=11.14$, $P<0.01$] decrements between 30 and 60 min post exercise. The maximal drop in MAP occurred 45 min post exercise and was ~7 mmHg (86±10 vs. 79±10). Again, this reduction was independent of exercise duration.

Heart rate was greater [$F(2,24)=4.61$, $P=0.02$] during the 30 min of exercise trial compared to the 15 min of exercise trial. There was no difference in heart rate between the 30 and 45 min of exercise trial. Across all trials, heart rate was elevated [$F(6,72)=72.07$, $P<0.01$] to 96 (±12) beats per min (BPM) at 5 min post exercise above the resting value of 70 (±9) BPM and steadily declined until 60 min post exercise, at which point it had returned to pre-exercise levels. $\dot{V}O_2$ was elevated [$F(6,72)=20.60$, $P<0.01$] for 5 min post exercise in all 3 trials and had returned to pre-exercise values by 10 min post exercise.

During the 45 min trial, haematocrit (Hct) increased [$F(9,81)=11.22$, $P<0.01$] above pre-exercise values during the initial 15 min of exercise (45.3±1.8% vs.

48.7±1.9%). This haemoconcentration persisted until 5 min post exercise (47.8±1.9%), but thereafter Hct did not differ from pre exercise values.

Study #2 - the effects of 10 and 30 minutes of exercise

The blood pressure response following exercise is illustrated in Fig. 2. SBP was significantly [$F(6,42)=5.01$, $P<0.01$] lower than baseline for the entire hour post exercise. Although the decline in SBP tended to be greater at all time points following the 30 min trial, this difference was not statistically significant [$F(6,42)=1.88$, $P>0.05$]. The maximum decrease in SBP was 14 mmHg at 15 min post exercise (133±8 vs.119±14). DBP was reduced [$F(6,42)=2.76$, $P=0.02$] at 5 min and 15 through 45 min post exercise. The nadir for DBP was ~8 mmHg lower than baseline (79±11 vs. 71±10) and occurred at 15 min post exercise. Again, although the decline in DBP tended to be greater following the 30 min trial, this was statistically independent of exercise duration [$F(6,42)=1.00$, $P>0.05$. MAP was below [$F(6,42)=3.35$, $P<0.01$] pre-exercise values for the entire hour post exercise, with the greatest reduction occurring at 15 min post exercise (96± 0.7 vs. 86±12 mmHg).

************Figure 2 About Here************

Heart rate remained significantly elevated [$F(6,42)=64.44$, $P<0.01$] during the whole post exercise period. Although there were slight differences in post exercise heart rate between trials, these were not significant. $\dot{V}O_2$ was not different between trials and was elevated [$F(6,42)=16.19$, $P<0.01$] for 10 min post exercise. Thereafter it had returned to pre-exercise values.

DISCUSSION

These studies have documented that the duration of exercise does not play a significant role in determining the occurrence or the magnitude of PEH. The initial study indicated that each of 15, 30 and 45 min of cycle ergometry at 70% $\dot{V}O_{2\,Peak}$ elicit a similar hypotensive response in healthy young men. The second study found that 10 min of exercise is also sufficient to cause PEH. This is contradictory to earlier work by Bennett et al. [4], who suggested that, as the duration of the exercise increased, so did the magnitude of the hypotension. In their study, post exercise blood pressure was measured during a 3 min rest period between 10 min bouts of exercise, thus making it difficult to compare their data with those of the present study. We did, however, observe in both of the present studies that blood pressure was more stable or still declining at the end of the 1 h measurement period following the longer duration of exercise (i.e. 45 min in study 1 and 30 min in study 2) whereas it was increasing after the shorter exercise bouts. Thus, it is possible that the duration of exercise may affect the duration of the hypotension. Further work will be needed to investigate this possibility.

Our findings lend support to the numerous studies that have found PEH to occur following a variety of exercise durations [e.g. 5,6,7,8,9] and suggest that moderate intensity exercise of relatively short duration (i.e. 10 min) is sufficient to evoke a hypotensive response.

A number of previous studies have indicated that PEH does not occur in a normotensive population [7,8,9,12,13]. The initial investigation here, as well as previous work from our laboratory [5] has shown that normotensive individuals do experience decrements in resting pressure after an acute bout of exercise. However, subjects in study

2 of the present investigation had higher resting blood pressure and the magnitude of their post exercise hypotension was greater than the subjects in study 1. This is in agreement with the literature suggesting that the hypotension following exercise is greater in those individuals with higher initial blood pressure [14].

In study 1, the fact that heart rate was elevated during the 30 min trial as compared to the 15 min trial was most likely attributable to cardiac drift and the proportion of time required to reach steady state in each trial.

Since haematocrit had returned to resting levels by 10 min post exercise and the hypotension persisted well beyond this in both studies, a shift of plasma volume causing a decreased total blood volume and subsequent drop in pressure does not appear to be responsible for the PEH. We have also examined the possibility that a static body position alone (i.e. independent of exercise) may have contributed to the PEH which is observed following exercise. Using both Finapres and intra-arterial monitoring of blood pressure, we have concluded that 75 min of quiet sitting on its own, when not preceded by exercise, has no effect on resting blood pressure [5, MacDonald, J.R. & MacDougall, J.D., unpublished observation]. The present study has documented that 10 min of exercise is sufficient to elicit post exercise hypotension. Although more work is required to determine the duration of the post exercise hypotension with each exercise duration, it appears that only a brief duration of exercise may act as a non-pharmacological aid to hypertension.

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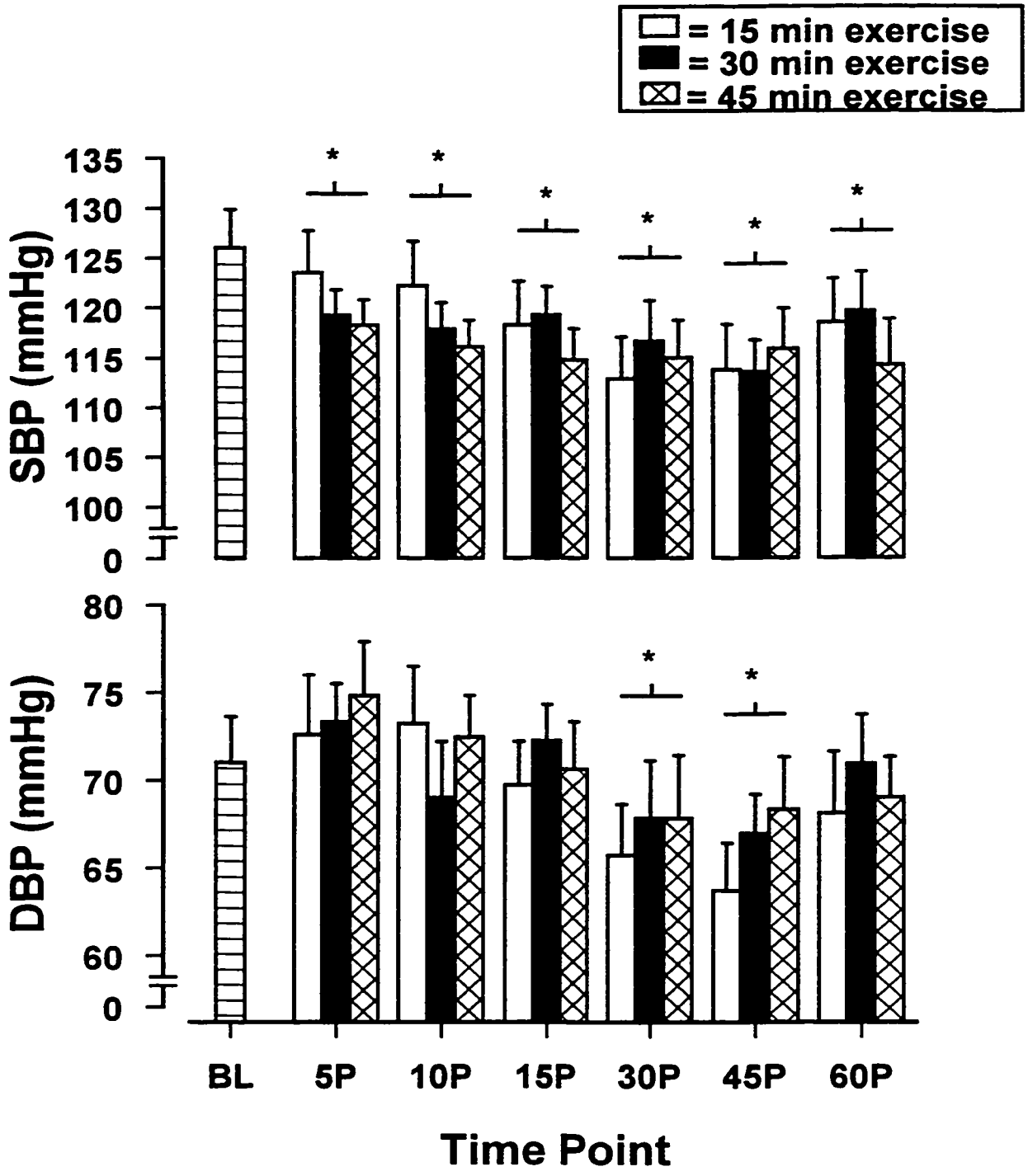
FIGURE CAPTIONS

Figure 1. The effects of exercise intensity at 70% of $\dot{V}O_{2peak}$ for 15, 30 and 45 min on post exercise blood pressure (mean±SEM). * indicates pooled data is significantly different from baseline. BL = baseline, P = min post exercise.

Figure 2. The effects of exercise at 70% $\dot{V}O_{2peak}$ for 10 and 30 min on post exercise blood pressure (mean±SEM). * indicates pooled data is significantly different from baseline. BL = baseline, P = min post exercise.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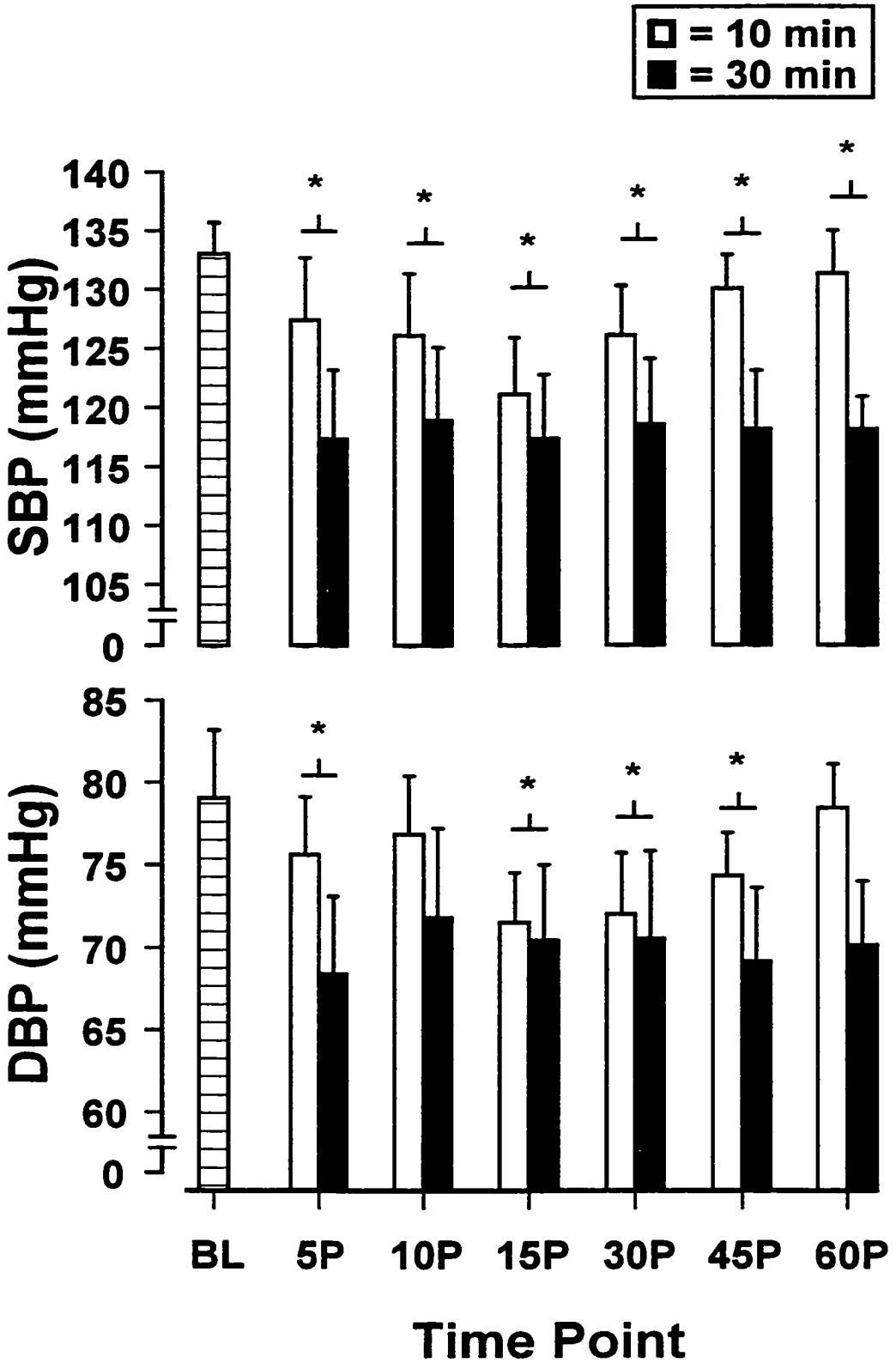
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70
65
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30P
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CHAPTER 5

The Effects Of Exercising Muscle Mass On Post Exercise Hypotension

THE EFFECTS OF EXERCISING MUSCLE MASS ON POST EXERCISE HYPOTENSION

MacDonald, J.R., J.D. MacDougall, C.D. Hogben. The effects of exercising muscle mass on post exercise hypotension. In press, *Journal of Human Hypertension*, 2000.

Jay R. MacDonald's Contribution:
a) study design
b) data collection
c) data analysis
d) manuscript preparation

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The assistance of Dr. J.D. MacDougall for his contributions in study design, manuscript preparation and study funding and of C.D. Hogben for his contributions to the data collection is gratefully acknowledged.

ABSTRACT

Nine recreationally active, borderline hypertensive subjects completed 30 min of arm ergometry (ARM) at 65% $\dot{V}O_{2\,Peak}$ and 30 min of leg ergometry (LEG) at 70% $\dot{V}O_{2\,Peak}$ (randomised order). Blood pressure was monitored before and for 1 hr after exercise using the Finapres method. Systolic, diastolic and mean blood pressure were significantly reduced for the entire 1 hr post exercise. This reduction was independent of exercise modality, but there was an indication for the duration of the effect to be prolonged following the leg exercise. We conclude that the mass of the working muscle does not directly effect the magnitude of post exercise hypotension (PEH) but may influence the duration of the response. These results suggest that a central mechanism or decreased vascular responsiveness is responsible for PEH.

Keywords: blood pressure, ergometry, Finapres

INTRODUCTION

The mechanism(s) responsible for post exercise hypotension (PEH) has not been established. Studies examining both peripherally [e.g. 1,2,3] and centrally [e.g. 4,5,6,7] mediated mechanisms have produced inconsistent results.

At the same relative percentage of limb specific $\dot{V}O_{2\,Peak}$, arm and leg ergometry are known to elicit similar blood pressure and heart rate responses [8]. It has been estimated that the mass of the upper limbs account for approximately 7.6% of the body's mass, whereas the lower limbs account for approximately 32% [9]. Thus at the same relative exercise intensity, the total active muscle mass and absolute metabolic rate would be greater for leg ergometry than for arm ergometry. It also follows that while intramuscular concentration of metabolites and ions (e.g. adenosine and K^+) would be similar for the 2 modes of exercise, the absolute production of these vasodilator substances and release into the circulation would be greatest with leg ergomety. Therefore, one might hypothesise that if PEH is mediated by some peripheral factor, leg ergometry would be expected to result in a greater decline in blood pressure. It was felt that by examining the influence of the exercising muscle mass, some insight may be provided as to the mechanism responsible for PEH.

METHODS

Subjects

Nine recreationally active participants (7 males, 2 females), with borderline hypertension (5 screening measurements of 135>SBP<150 and/or 85>DBP<95) volunteered to participate in this study. Subjects had a mean age of 23±4 (mean±SD) years, a mean height of 176±13 cm and a mean weight of 77.4±7.5 kg. Average body

mass index was similar between the males (24.74) and females (24.67) and listed within the "healthy range" [10]. The McMaster University Human Ethics Committee approved the study and subjects were advised of the risks before providing written informed consent.

Preliminary Testing

The Finapres system was used to measure blood pressure in this study. We have recently discussed the accuracy of the Finapres during resting measures following exercise. The reader is referred to reference 11 for this discussion. On 5 separate days, participants were required to undergo resting Finapres blood pressure measurement after a seated period of 20 - 30 min. The five systolic and five diastolic blood pressures were averaged and 1 standard deviation was calculated. If, during one of the experimental trials, initial resting pressure (either systolic or diastolic) was not within 1 standard deviation of the subject's pre trial average, the test was terminated and rescheduled for another day.

Prior to beginning the study, limb specific maximal oxygen uptake was determined using incremental arm and leg ergometry tests to exhaustion. Both tests used an electrically braked cycle/arm ergometer (Eric Jaeger, Hoechberg, Germany). During each test, subjects exercised at a cadence greater than 60 revolutions per min (rpm). At the completion of each 2 min interval, the power output was increased by 20-60 Watts, dependent on the limbs used and state of fatigue. Volitional exhaustion was deemed to be the point at which subjects could no longer maintain a cadence of 60 rpm. The mean of the two consecutive highest oxygen uptake values was considered the limb specific $\dot{V}O_{2\,Peak}$. Expired gas was collected using a one-way air flow valve (Hans Rudolph

#2700, Hans Rudolph Inc., Kansas City Mo.) and analysed on line via an IBM compatible computer using the TurboFit software package (Vacumetrics, Ventura, Ca.) coupled with and AMETEK S3A/1 oxygen analyser (Applied Electrochemistry, Pittsburg, Pa.) and a Hewlett Packard 78356A carbon dioxide analyser (Hewlett Packard, Mississauga, Ont.). Both analysers were calibrated prior to and following each test using gases of known O_2 and CO_2 content.

Limb specific $\dot{V}O_{2\ Peak}$ was 30.96 $mL \cdot kg^{-1} \cdot min^{-1}$ for arm exercise (ARM) and 46.81 $mL \cdot kg^{-1} \cdot min^{-1}$ for leg exercise (LEG). Although the original intent was to have subjects perform each exercise session at 70% of limb specific $\dot{V}O_{2\ Peak}$, initial trials demonstrated that most subjects could only maintain arm ergometry at 65% of $\dot{V}O_{2\ Peak}$. Therefore a revised 65% and 70% of the limb specific $\dot{V}O_{2\ Peak}$ was calculated for the ARM and LEG trials respectively as the target oxygen consumption during the submaximal exercise trials.

Subjects refrained from exercising during the 24 hours prior to testing and consumed no stimulants or depressants known to affect blood pressure (e.g. caffeine and alcohol).

Protocol

After a 4 h fast, the subjects reported to the laboratory and remained quietly seated for 30 min. They then underwent resting Finapres blood pressure measurements verified by auscultation. The Finapres transducer was placed at mid-sternal level and coupled to an on-line data acquisition package (Windaq/200, DataQ Instruments Inc., Akron, OH) sampling at a frequency of 300 Hz. Calibration of the Finapres was completed using an internal calibration sequence as well as a mercury manometer. The

transducer was calibrated to show a linear response between 0 and 300 mmHg. On separate days, subjects were required to perform 30 min of arm ergometry at a power output that elicited 65% of arm $\dot{V}O_{2\,Peak}$, and 30 min of leg ergometry at a power output that elicited 70% of leg $\dot{V}O_{2\,Peak}$ (randomised order).

Finapres blood pressure was monitored continuously throughout the session with 2 min windows recorded at rest, 5, 10, 15, 30, 45 and 60 min post exercise for subsequent analysis.

Analysis

Blood pressure waveforms were analysed using the Windaq data analysis software (DataQ Instruments Inc., Akron, OH). Systolic (SBP) and diastolic (DBP) blood pressure were calculated as the highest point in the waveform and the lowest point in the waveform prior to the last inflection point, respectively. Mean arterial pressure (MAP) was determined by the quotient of the integrated pressure and the duration of the time interval.

All blood pressure variables were assessed using single, 2 factor, repeated measures, analyses of variance (ANOVA) with trial and time of measurement as the repeated measures. The Tukey Honestly Significant Difference (HSD) method was used to identify the location of any significant differences. A probability level of $p \leq 0.05$ was considered statistically significant. All values are expressed as mean ± standard deviation unless otherwise stated.

RESULTS

The effects of exercise on post exercise blood pressure are illustrated in Fig. 1. No differences were found between ARM or LEG trials. Collectively, SBP was

significantly [F(6,48)=5.64, P<0.01] reduced from pre-exercise values between 5 and 60 min post exercise inclusive. The pressure decrement was constant at ~15 mmHg below pre-exercise values (140±12 mmHg) for the entire post exercise monitoring. DBP was also decreased for the entire post exercise period [F(6,48)=3.28, P<0.01]. The nadir of DBP occurred at 45 min post exercise (82±13 vs. 73±11) and collectively, fluctuated no more than 3 mmHg during the post exercise period.

************Figure 1 About Here – SBP & DBP ***********

MAP also remained below pre-exercise values for the entire hour post exercise [F(6,48)=3.70, P<0.01]. The maximal drop in MAP was 10 mmHg (99±14 vs. 89±14 mmHg) at 30 min post exercise. Collectively, MAP remained 8 mmHg below baseline values at the end of the 1 hour measurement period.

In this borderline hypertensive population, which was prone to large fluctuations in blood pressure, the baseline blood pressure varied by 6 and 7 mmHg for SBP and DBP respectively with subjects having higher blood pressures prior to ARM exercise. We therefore felt it necessary to analyse changes in blood pressure relative to pre-exercise values (delta scores) to confirm the results found with the absolute blood pressure data. As shown in Fig. 2, the delta scores confirm that blood pressure is significantly decreased for the entire post exercise period. Additionally, with the baseline delta scores excluded, at sixty minutes post exercise, systolic [F(5,40)=2.57, P<.05] and mean arterial [F(5,40)=3.80, P<.01] blood pressures are significantly lower after LEG exercise as compared to ARM exercise. This may suggest that there is no difference in the magnitude of PEH found after ARM or LEG exercise, but the duration of the PEH may be influenced by the exercise intervention.

************Figure 2 About Here – Difference Scores************

DISCUSSION

We have recently documented that there are no blood pressure changes resulting from 75 minutes of seated rest [1]. We are therefore confident that the decrements in blood pressure documented here are a result of the exercise interventions. This study indicates that the magnitude of the decrement in post exercise blood pressure is not influenced by the mass of the working muscle. This would lend support to two theories of post exercise hypotension. Firstly, PEH may be mediated by factors originating in the brain and cardiovascular control centres. Rodent work has suggested that the central opioid and serotonergic systems, leading to changes in sympathetic activity may be the source of PEH [6,7,14]. However, studies examining these systems in humans are contradictory [4,5] and have not been pursued in recent years. Secondly, there is some evidence to suggest that an exercise induced decrease in vascular sensitivity may be responsible for PEH. The data presented in Fig. 2 suggests that the duration of the hypotension may be influenced by the exercising muscle mass since the blood pressure was declining after 30 min of seated rest following the LEG trial whereas it had begun to return towards baseline at the same time following the ARM trial. Although there are no differences in the magnitude of PEH found after arm and leg ergometry in the present study, the possibility exists that there may be a saturation at some rate limiting step moderating the PEH. It is possible that such a saturation could be responsible for a longer duration of PEH. Previous work examining vascular sensitivity following exercise has suggested that a decline in the vascular sensitivity may be responsible for the observed drop in blood pressure in humans [15]. Further experimental work in animals

has also suggested such a link. Using excised aortic rings from the New Zealand white rabbit, reduced α-adrenergic mediated isometric tension was observed following exercise [16]. Subsequently, decreased iliac blood flow mediated by adrenergic receptor sensitivity was found in an isolated preparation of the rat hind-limb [17]. Although no PEH was observed in that study and the reduced sensitivity could be related to numerous factors, inhibition of nitric oxide attenuated the decreased sensitivity after exercise, suggesting that nitric oxide may, at least partly be responsible for the decreased sensitivity post exercise. Using ganglionic blocked, intact, Dahl salt sensitive rats, VanNess et al. [18] found an exercise induced attenuation in blood pressure responsiveness to the α-adrenergic agonist phenylephrine until the cessation of measurement at 30 minutes post infusion. Reduced vascular responsiveness in humans by any of numerous factors, and in particular, nitric oxide, has yet to be investigated but remains an interesting possibility.

Given these previous reports and the data presented here, future work in determining the mechanisms for PEH should therefore focus on changes in vascular sensitivity and central factors including the opioid and serotonergic systems.

ACKNOWLEDGEMENTS

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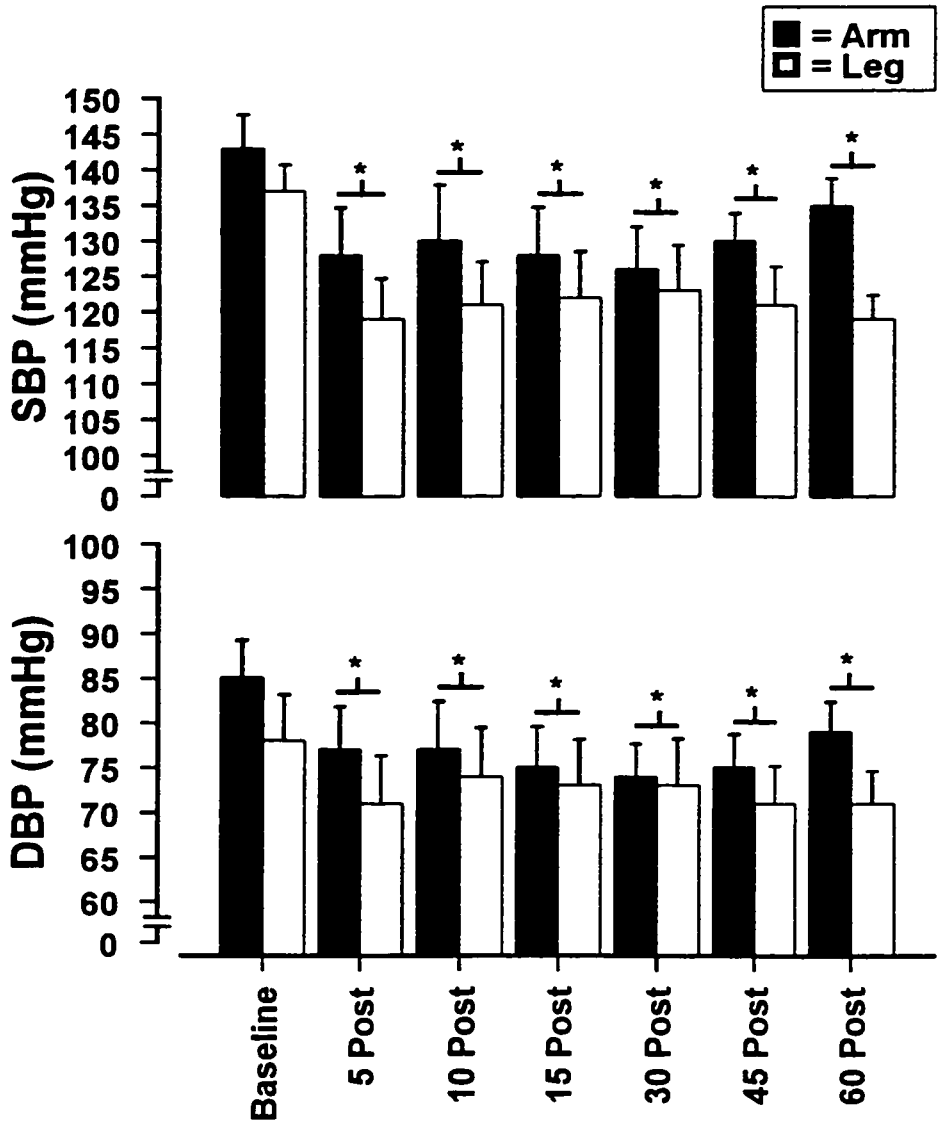
FIGURE CAPTIONS

Figure 1. The effects of 30 min of arm and leg exercise on post exercise blood pressure (mean±SEM). * indicates pooled data is significantly different from baseline. Post = min post exercise.

Figure 2. Changes in blood pressure following 30 min of arm or leg exercise. * indicates pooled data is significantly different from baseline. τ indicates ARM and LEG values differ from each other (baseline data excluded). Post = min post exercise.


■ = Arm
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SBP (mmHg)
150
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DBP (mmHg)
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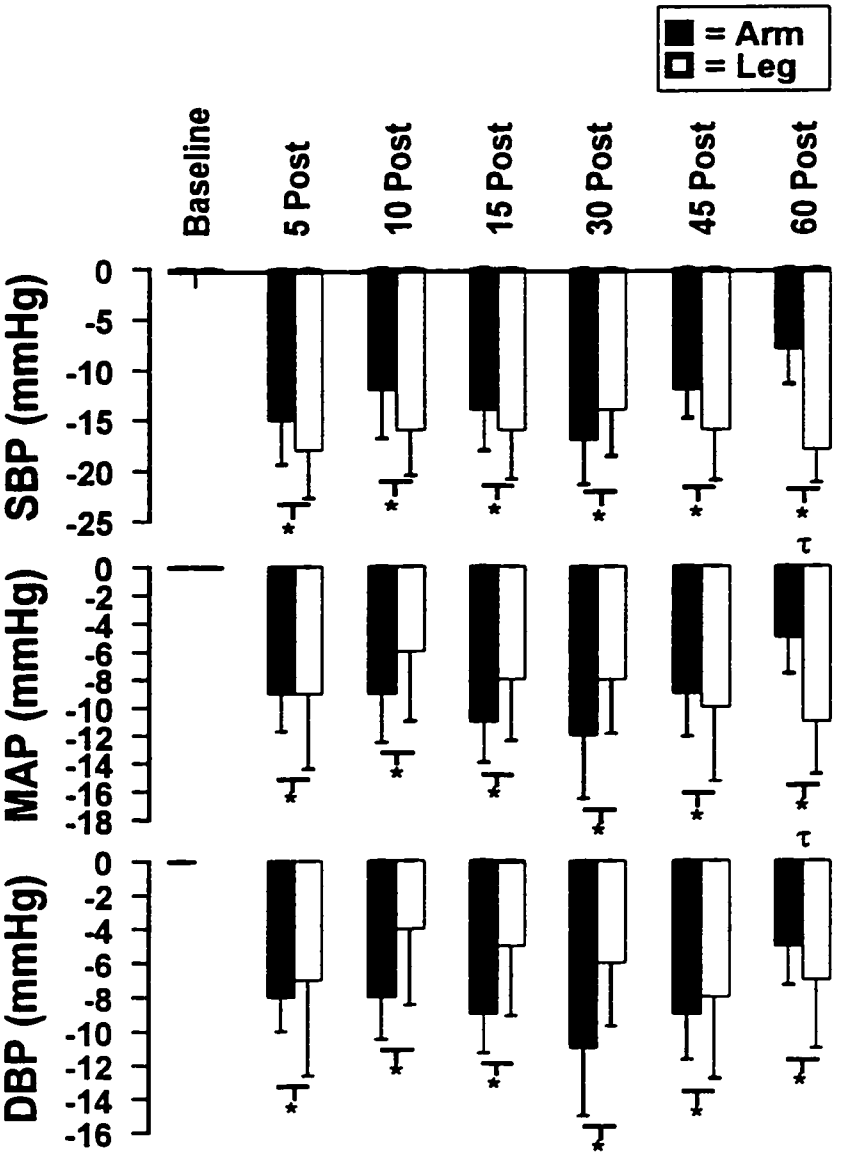
■ = Arm
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Baseline
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SBP (mmHg)
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MAP (mmHg)
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DBP (mmHg)
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CHAPTER 6

Post Exercise Hypotension Is Sustained During Subsequent Bouts Of Mild Exercise And Simulated Activities Of Daily Living

POST EXERCISE HYPOTENSION IS SUSTAINED DURING SUBSEQUENT BOUTS OF MILD EXERCISE AND SIMULATED ACTIVITIES OF DAILY LIVING

MacDonald, J.R., J.D. MacDougall, C.D. Hogben, M.A. Tarnopolsky. Post exercise hypotension is sustained during subsequent bouts of mild exercise and simulated activities of daily living. In submission.

Jay R. MacDonald's Contribution:
a) study design
b) data collection
c) data analysis
d) manuscript preparation

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ABSTRACT

Objective: The purpose of this investigation was to examine the acute effects of prior exercise on blood pressure during subsequent mild exercise and simulated activities of daily living (ADL) using direct measurements of arterial pressure.

Methods: Eight recreationally active participants, with low borderline hypertension completed 30 min of cycle ergometry at 70% $\dot{V}O_{2Peak}$ and 30 min of quiet seated rest on separate days (randomised order). Following exercise and rest, subjects completed a 70 min protocol of mild exercise and simulated activities of daily living (ADL). Blood pressure was monitored throughout using direct arterial measurement.

Results: Exercise resulted in lower systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) throughout the post exercise ADL period compared to those measurements taken without prior exercise. The maximal difference in SBP, DBP and MAP between trials was 26, 7 and 13 mmHg respectively. This relative hypotension occurred in spite of higher heart rates during the ADL measurement period following the prior exercise. Furthermore, many of the blood pressure measurements during the post exercise period were significantly lower than the pre exercise values during the same trial.

Conclusion: We conclude that post exercise hypotension persists during mild exercise and simulated activities of daily living. Although the duration of this hypotension needs to be determined, acute exercise may serve as a non-pharmacological aid in the treatment of hypertension.

Keywords: post exercise hypotension; intra-arterial pressure; exercise; anti-hypertensive agents

INTRODUCTION

In addition to the moderating effect that endurance exercise training has on the blood pressure of hypertensive individuals, a growing body of literature suggests that acute bouts of exercise may also have a transient effect on lowering blood pressure, for at least several hours following the exercise. This phenomenon has been termed post exercise hypotension (PEH). Most previous studies have documented PEH during seated or supine rest following exercise (1,2,3) but we are aware of six that have attempted to examine whether the hypotension is preserved during subsequent mild exercise or routine daily activities (4,5,6,7,8,9). Results from these studies are contradictory and somewhat confounded by the fact that, following exercise, activity was not controlled and that the investigators used auscultatory methods to determine blood pressure. Given the great differences in blood pressure between rest and activity and the influences of the breathing cycle and other cyclic waves on blood pressure, these auscultatory methods are prone to sampling error and may provide inaccurate or inconsistent results. Of the studies examining ambulatory, post exercise blood pressure, three have failed to address the influences of diurnal variation in blood pressure by only comparing post-exercise blood pressure to a pre-exercise control value (5,6,8). In a free living environment, those studies comparing post exercise blood pressure to blood pressure following a control period of rest may also be misleading, in that a bout of exercise may induce a more sedentary period post exercise (4,7,9).

Therefore, the purpose of this investigation was to examine the effects of prior exercise on blood pressure during mild exercise and simulated activities of daily living (ADL) using direct measurements of arterial pressure. Given that nutritional changes and

exercise are first line strategies in the treatment of mild hypertension, it is important to accurately characterise the efficacy of these. From a practical standpoint, the PEH phenomenon will have clinical utility only if the relative hypotension is sustained during activities of daily living.

METHODS

Subjects

Eight recreationally active participants (6 males (M), 2 females (F)), with low borderline hypertension (143±9 / 73±6 mmHg) volunteered to participate in this study. Subjects had a mean age of 23±4 (mean±SD) years, a mean height of 177±12 cm (F= 165±4, M=182±11) and a mean weight of 79±4 kg (F= 67±6, M=81±3). The McMaster University Human Ethics Committee approved the study and subjects were advised of the risks before providing written informed consent.

Preliminary Testing

Subjects' maximal aerobic power ($\dot{V}O_{2Peak}$) was assessed by a standard continuous progressive loading protocol on an electrically braked cycle ergometer (Eric Jaeger, Hoechberg, Germany). Expired gases were measured using a computerised open circuit gas collection and analysis system. Expired gases were collected and oxygen consumption was calculated every 30s during the test until fatigue. $\dot{V}O_{2Peak}$ was determined as the highest oxygen consumption (averaged over 1 min) achieved during the test. Details of this testing have been previously described (10).

Protocol

Subjects reported to the laboratory after a four hour (h) fast on two separate occasions separated by at least one week. During the 36 h preceding each trial, ingested

food was kept constant between trials by having the subjects consume identical meals and portions. Diet was free from any stimulants or depressants known to affect blood pressure (e.g. caffeine and alcohol). Additionally, no formal exercise was performed during this period. Upon arriving at the laboratory, a 3.8 cm, 20 gauge catheter was inserted into the radial artery and coupled to a saline-Heparin (1000mL:500units) (Wyeth-Ayerst, Toronto, Ontario) drip, equipped with a pressure transducer (Novotrans, MX 800, Medex Inc., Hilliard, Ohio) for the direct measurement of blood pressure. This transducer was placed at mid-sternal level and coupled to an amplification system (Acudata, model 143, Honeywell Inc., Denver, Colorado) and an on-line data acquisition package (Windaq/200, DataQ Instruments Inc., Akron, Ohio) sampling at a frequency of 300 Hz. Calibration of the pressure monitoring system was completed using a mercury manometer before each individual trial. The system was calibrated to show a linear response between 0 and 300 mmHg. Subjects then remained in a seated, resting position for a minimum of 30 min before the collection of baseline measurements. After a 5 min recording of baseline blood pressure and heart rate, subjects completed either 30 min of cycling at a power output eliciting 70% of $\dot{V}O_{2Peak}$, or 30 min of quiet, seated rest (randomised order).

After cycling or rest, the participants then engaged in a 70 min protocol of mild exercise and simulated activities of daily living (ADL). This protocol was comprised of 5 min of seated rest (1-sit), 5 min of quiet standing (2-stand), 10 min treadmill walking at 4.8 kilometres per hour (Km/h)(3-walk), 15 min of seated rest (4-sit), 10 min of cycle ergometry at 100 Watts (5-cycle), 5 min of treadmill walking at 4.8 Km/h (6-walk), 5 min seated rest (7-sit), 5 min of treadmill walking at 4.8 Km/h and carrying a 5.7 kg briefcase

(8-wtwalk) and 10 min of seated rest (9-sit). These were specifically chosen to mimic some of the more common activities of daily living that may be encountered. Blood pressure was continuously monitored for the entire trial and averaged over each segment of activity. Heart rate was recorded at three equidistant times during each segment and the average was taken as the heart rate for that segment. The two trials were performed at the same time each day and laboratory temperature and humidity was kept constant for each trial (23°C, 70% relative humidity).

Analysis

Blood pressure waveforms were analysed using the Windaq data analysis program (DataQ Instruments Inc., Akron, OH). SBP and DBP were calculated as the highest point and lowest point prior to the last inflection point in the waveform, respectively. The quotient of the integrated pressure and the duration of the time interval determined mean arterial pressure (MAP).

Power Spectral Analysis of Heart Rate Variability (HRV)

To assess the potential contribution of the autonomic nervous system to PEH, power spectral analysis of HRV was employed. For a review on this procedure, the reader is referred to reference #11. Briefly, the time series of the HR data were linearly interpolated on an xy series to a standard interval series that can be numerically processed using standard fast fourier transformation (FFT) techniques. Data were then filtered using a lowpass Butterworth filter followed by a Hammond window. Power spectral density was calculated and then integrated and normalised. Data falling above 0.15 Hz was considered high frequency, and data falling below 0.15 Hz was considered low frequency. The low frequency area to high frequency area (LF:HF) was calculated and

considered indicative of relative changes in sympathetic activity. The high frequency to total area (HF:Total) was calculated as an index of parasympathetic activity.

Statistical Analysis

All data were analysed using one-way, repeated measures analyses of variance (ANOVA) (Statistica, Statsoft, Tulsa, OK). Significant findings were assessed using the Tukey honestly significant difference post hoc comparison. All values are expressed as means ± SD unless otherwise noted.

RESULTS

The effects of exercise on SBP are summarised in Fig. 1. Exercise resulted in a significant difference ($p=0.01$) between trials. SBP was 158±9 mmHg during the rest only trial and 144±12 mmHg during the prior exercise trial collapsed across resting and post exercise ADL measurements. The decrement in post exercise blood pressure between the rest and exercise trials was significant ($p<0.01$) at all times, with the post exercise measurements being lower than those after seated rest. The greatest difference between trials was 26 mmHg and occurred during quiet standing at 5 min post exercise. The average difference in SBP during the 70 min post exercise ADL monitoring was 16 mmHg. Prior exercise also elicited an absolute drop in SBP from baseline at 5 of the 9 post exercise measurements. During the post exercise ADL periods of sitting and standing (1-sit, 2-stand, 4-sit, 7-sit, 9-sit), blood pressure was consistently between 12 and 17 mmHg below baseline values.

**********Figure 1 About Here**********

DBP exhibited a similar pattern as illustrated in Fig. 2. After exercise, blood pressure was significantly lower ($p<0.01$) than the non-exercise trial during 7 of the 9

post exercise ADL measurements. Only 5-cycle and 6-walk failed to reach significance, although lower than in the control trial. The maximum difference occurred during seated rest (4-sit) and was 7 mmHg below the non-exercise control value at the same time point. The average between trials reduction in DBP after exercise was 5 mmHg. During the periods of seated rest, DBP was also reduced from baseline during the prior exercise trial. The average decrement from baseline during seated rest (1-sit, 4-sit, 7-sit and 9-sit) was 5 mmHg.

**********Figure 2 About Here**********

Average MAP following the rest only trial was 99±6 mmHg and 91±7 mmHg following the prior exercise trial. As shown in Fig. 3, post exercise ADL measurements were significantly ($p<0.01$) depressed at all time points as compared to the non-exercise control values at similar time points. The average decrease in the post exercise ADL period was 8 mmHg with a nadir of 13 mmHg occurring during the second period of seated rest (4-sit). MAP was also reduced from baseline values in the prior exercise trial at the sitting and standing measurements (1-sit, 2-stand, 4-sit, 7-sit, 9-sit) by 5 – 8 mmHg.

**********Figure 3 About Here**********

Across all time points, heart rate was significantly higher during the prior exercise trial by 18 beats per min (bpm) (82±10 vs. 99±11 bpm). Collapsed across trials, the heart rate was significantly ($p<0.01$) higher than baseline measures at all time points (Fig. 4).

HRV data showed no differences between trials with respect to the LF:HF data. However, a significant ($p<0.01$) decrease from baseline in the LF:HF data at the 5-walk and 6-cycle trials was found across both trials ($p<0.01$). Across both trials, the HF:Total ratio was significantly ($p<0.01$) increased from baseline during the following time points:

3-walk, 5-cycle, 6-walk and 8-wtwalk. Additionally, there was a significantly greater HF:Total ratio during the pre-exercise trial at the 3-walk and 6 walk time points as compared to the same time points during the non-exercise control trial.

DISCUSSION

Indwelling blood pressure measurements indicated that post exercise SBP, DBP and MAP were significantly lower when preceded by prior exercise compared to non-exercise control measurements. This decrement persisted throughout the 70 min monitoring period of mild exercise and activities including sitting, standing, cycling, and walking with and without weights.

Previous studies have attempted to evaluate the post exercise hypotensive response during activity, but have used different blood pressure monitoring devices between the pre and post exercise measurements and did not control the activity during the post exercise monitoring period (4,5,6,7,8,9). In those studies that have examined the possibility of prolonged PEH (over a 12-24 h period) (4,5,7,8,9) the varied activity by participants between rest and exercise trials, and the fact that a bout of exercise may induce a more sedentary post exercise period complicates the interpretation of that data and may contribute to the contradictory results. In all cases, blood pressure was monitored at intervals greater than, or equal to, every 15 minutes. Because of the oscillatory nature of arterial blood pressure, sampling at these frequencies may not have accurately reflected the true blood pressure. Although some have found prolonged blood pressure decrements after exercise (5,7,9), many studies have suggested that PEH may not persist longer than 1-2 h (5,12,13). In a controlled setting and using direct blood pressure measurements, our results indicate that the decrements in SBP, DBP, and MAP

remained significant to the end of the 70 min post exercise ADL monitoring period with no trend towards returning to pre exercise values.

In the present study, prior exercise attenuated the blood pressure response to subsequent mild exercise in spite of the fact that HR was higher throughout this period, compared to the control condition. Possible mechanisms that might cause PEH include a reduction in sympathetic efferent activity (12) and/or a decreased peripheral resistance in skeletal muscle and other vascular beds (2,14). Our finding that HR was significantly higher following the prior exercise condition and, more directly, that there was no difference between trials in the HRV indicative of SNA suggested that sympathetic efferent activity was not decreased during the period over which the hypotension occurred. Previous studies using borderline hypertensive subjects have also used a subject population at the lower end of the spectrum (SBP = 135 – 144 mmHg) (3,5,6,12). The maximal systolic blood pressure reductions found in those studies were between 9 and 13 mmHg. The maximal decrement in the present study was 17 mmHg as compared to baseline and 26 mmHg relative to the control trial. This study confirms the occurrence of PEH in this borderline hypertensive population. This disparity of magnitude between studies may be due to the ability of the indwelling catheters to more accurately measure pressure changes. Although reports of diastolic hypotension are not always evident following exercise, we found that prior exercise lowered diastolic pressure by an average of 5 mmHg (both absolute compared to baseline and relative compared to no prior exercise control measurements) and at times as much as 7 mmHg below control measurements over the 70 min post exercise period. Using a similar population, Hara & Floras (6) noted a 6 mmHg drop in DBP during supine rest at 1 h post exercise. Other

studies have shown no decrement in DBP (5,12). Given the day to day blood pressure variability often found in borderline hypertensives, which is often more evident in DBP, these contradictory results may be due to the inter-trial variance.

Overall, the results of this study indicate that a relatively brief period of exercise can result in a lower blood pressure during subsequent physical activity than a control condition where no prior exercise is performed. Importantly, this relative (and often absolute) hypotensive effect is apparent even during activities of daily living. Although we saw a persistence of this effect for 70 min, future work needs to examine the duration of this decreased pressure.

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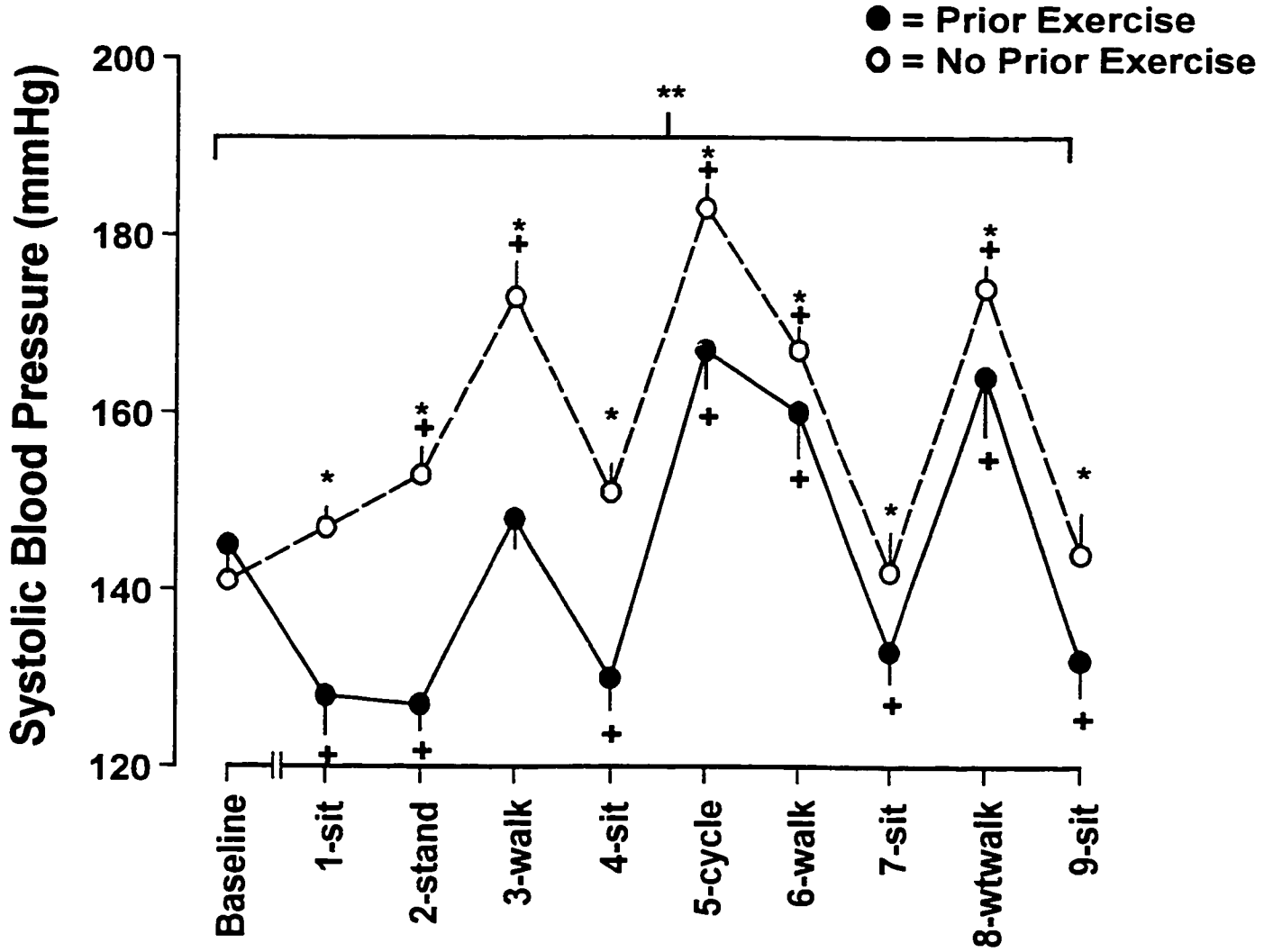
FIGURE CAPTIONS

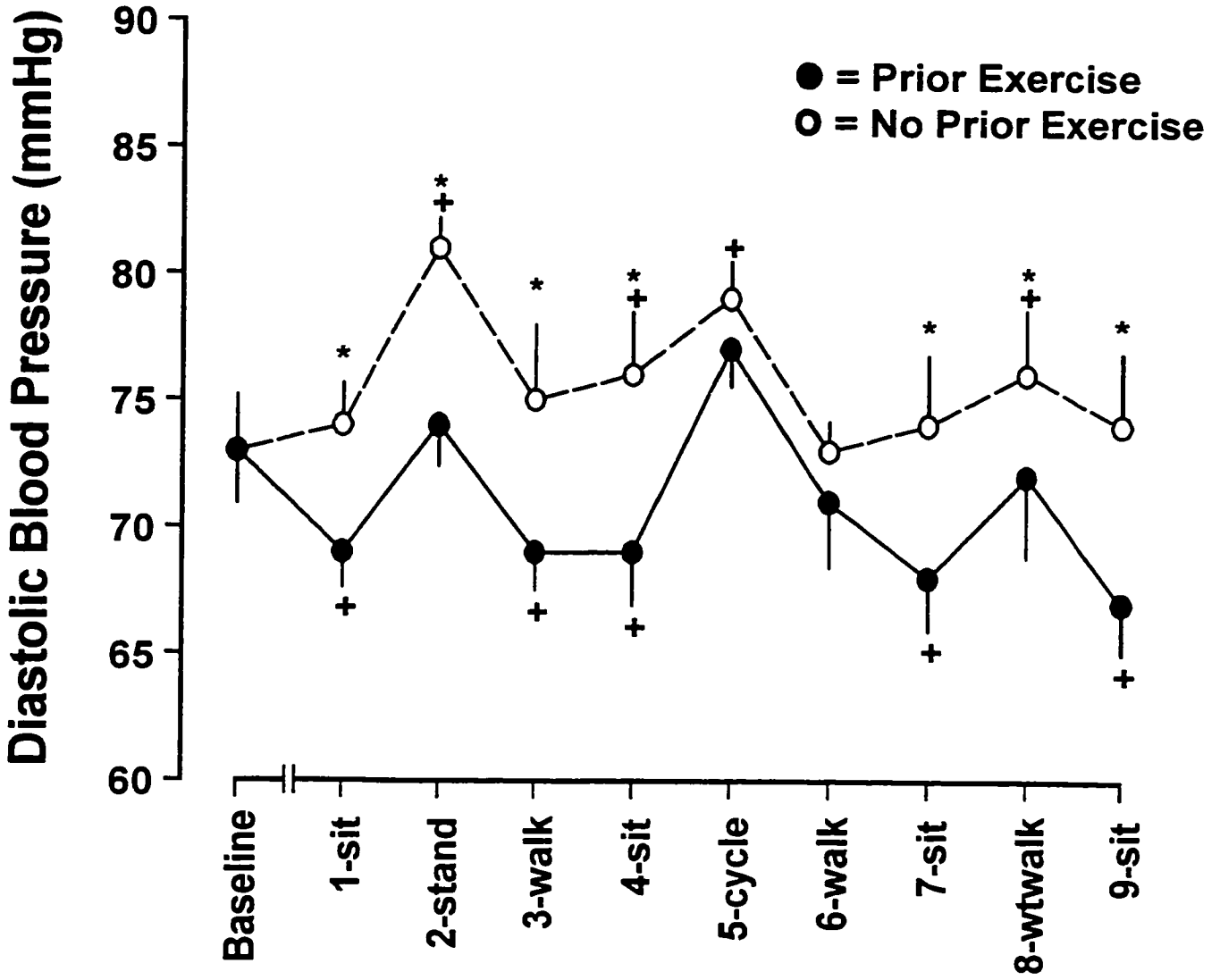
Fig. 1. The effects of prior exercise on SBP during subsequent mild exercise and simulated activities of daily living (mean±SEM). * = prior exercise trial different from non-exercise control; ** = prior exercise trial main effect significantly different from control trial; + = different from trial baseline.

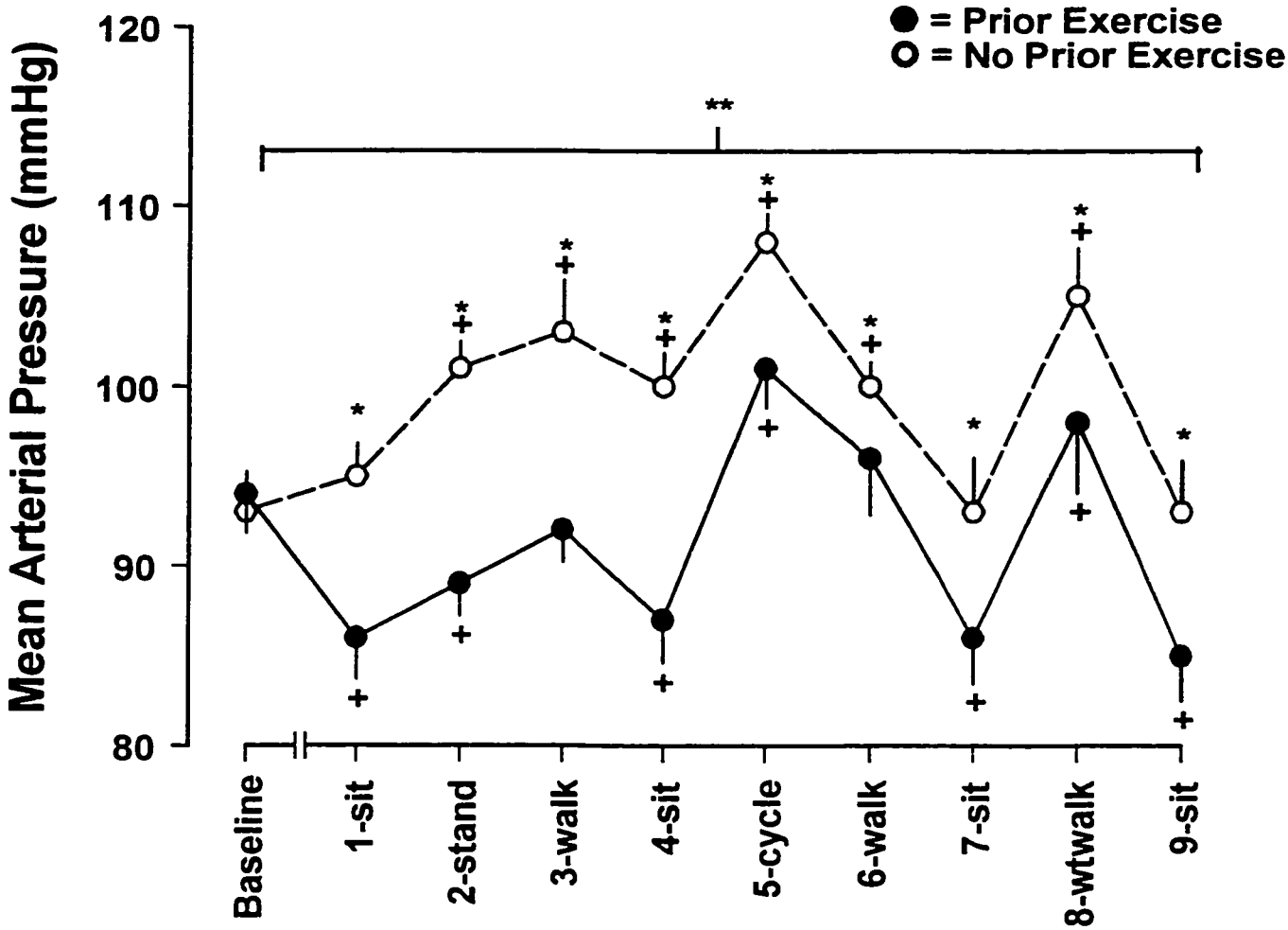
Fig. 2. The effects of prior exercise on DBP during subsequent mild exercise and simulated activities of daily living (mean±SEM). * = prior exercise trial different from non-exercise control; + = different from trial baseline.

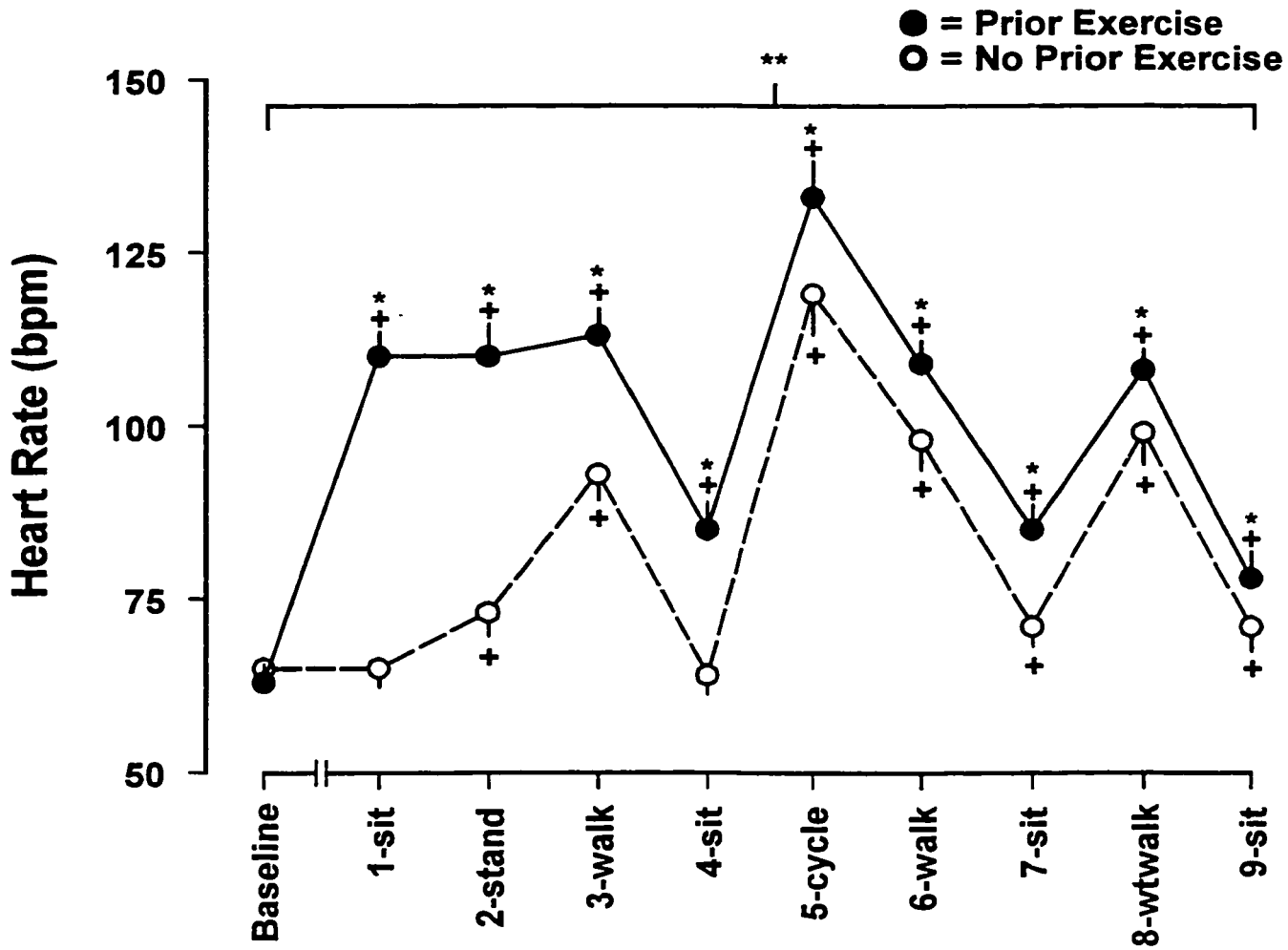
Fig. 3. The effects of prior exercise on MAP during subsequent mild exercise and simulated activities of daily living (mean±SEM). * = prior exercise trial different from non-exercise control; ** = prior exercise trial main effect significantly different from control trial; + = different from trial baseline.

Fig. 4. The effects of prior exercise on HR during subsequent mild exercise and simulated activities of daily living (mean±SEM). * = prior exercise trial different from non-exercise control; ** = prior exercise trial main effect significantly different from rest trial; + = different from trial baseline.


● = Prior Exercise
O = No Prior Exercise
Systolic Blood Pressure (mmHg)
200
180
160
140
120
**
Baseline
1-sit
2-stand
3-walk
4-sit
5-cycle
6-walk
7-sit
8-wtwalk
9-sit


Diastolic Blood Pressure (mmHg)
90
85
80
75
70
65
60
● = Prior Exercise
O = No Prior Exercise
Baseline
1-sit
2-stand
3-walk
4-sit
5-cycle
6-walk
7-sit
8-wtwalk
9-sit


● = Prior Exercise
○ = No Prior Exercise
Mean Arterial Pressure (mmHg)
120
110
100
90
80
**
Baseline
1-sit
2-stand
3-walk
4-sit
5-cycle
6-walk
7-sit
8-wtwalk
9-sit


● = Prior Exercise
O = No Prior Exercise
**
Heart Rate (bpm)
150
125
100
75
50
Baseline
1-sit
2-stand
3-walk
4-sit
5-cycle
6-walk
7-sit
8-wtwalk
9-sit

CHAPTER 7

Post Exercise Hypotension Is Not Mediated By The Serotonergic System In Borderline Hypertensive Individuals

POST EXERCISE HYPOTENSION IS NOT MEDIATED BY THE SEROTONERGIC SYSTEM IN BORDERLINE HYPERTENSIVE INDIVIDUALS

MacDonald, J.R., J.M. Rosenfeld, M.A. Tarnopolsky, C.D. Hogben, C.S. Ballantyne and J.D. MacDougall. Post exercise hypotension is not mediated by the serotonergic system in borderline hypertensive individuals. In submission.

Jay R. MacDonald's Contribution:
a) study design
b) data collection
c) data analysis
d) manuscript preparation

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ABSTRACT

Recent evidence from our laboratory and others have suggested that the mechanism for a decrease in resting blood pressure after an acute bout of exercise is mediated by central factors. This study examined the effect of the central serotonergic system on post exercise hypotension (PEH) in eleven borderline hypertensive individuals (9 male, 2 female) aged 24.5±5.1 years. Indwelling baseline blood pressure was 145/72 mmHg for systolic (SBP) and diastolic (DBP) respectively. Each subject completed 2 trials of a 30 min cycling protocol at 70% of $\dot{V}O_{2Peak}$ while under placebo or a selective serotonin reuptake inhibitor (SSRI) treatment. Testing was done in a double blind randomised order with a minimum of fourteen days between trials. Peripheral measures of serotonin (5-HT) were decreased under SSRI treatment, whereas the major 5-HT metabolite, 5-hydroxyindoleacetic acid, was not significantly changed, indicating elevated central 5-HT levels. There was no difference in any of the haemodynamic variables between trials. Despite an increased heart rate for the initial 75 min post exercise, SBP was decreased as much as 23 mmHg during the initial 60 minutes post exercise, after which it had returned to normal. DBP was unchanged after exercise. Circulating epinephrine (0.60±0.14 ng/mL to 1.3±1.6 ng/mL) and norepinephrine (0.27±0.31 ng/mL to 4.5±2.1 ng/mL) were significantly elevated during exercise. Both returned to pre-exercise levels within 15 minutes post exercise. Unexpectedly, oxygen uptake was slightly (5%), but significantly increased during SSRI treatment. We conclude that the central serotonergic system is not responsible for PEH in our borderline hypertensive population.

INTRODUCTION

A growing body of literature has confirmed that an acute bout of exercise can cause a decrease in the normal resting blood pressure that may last up to several hours. This phenomenon is particularly evident in hypertensive and borderline hypertensive individuals and has been coined post exercise hypotension (PEH). This decrease in blood pressure could be caused by a decrease in cardiac output ($\dot{Q}c$) or a decrease in total peripheral resistance (TPR) (or both). Since oxygen uptake ($\dot{V}O_2$) and heart rate (HR) have been shown to return to pre-exercise values during the post exercise hypotensive state (16) it is unlikely that there is a significant decrease in $\dot{Q}c$. This suggests that PEH is a function of decreased TPR.

A decrease in TPR can be the result of centrally mediated mechanisms (e.g. decreased efferent activity from the sympathetic nervous system (SNS)) or locally mediated vasodilation (e.g. in response to locally released metabolites and compounds). The finding that the magnitude of the PEH is largely independent of exercise intensity (13), exercise duration (14) or the size of the exercising muscle group (15) argues against a local mechanism. In addition, PEH persists long after body temperature, circulating exercise metabolites or ionic imbalances have returned to normal.

It has been hypothesised that exercise induced alterations in the opioid system may be a mechanism that centrally affects blood pressure (2). Although little is known about the mechanics of this system, it may moderate sympathetic activity (2). Specifically, ß-endorphins are known to increase during exercise, and are often claimed to be responsible for the sensation of euphoria that accompanies moderate intensity endurance exercise (9). Early work examining ß-endorphins and blood pressure found

that infusion of ß-endorphins resulted in a prolonged drop in blood pressure (12). Studies with humans, which have examined the contribution of the ß-endorphins to PEH, have yielded contradictory results when the opioid system was blocked with naloxone, an opioid receptor antagonist (2,7). It has been suggested that a chemical link may exist between the serotonergic system and the endorphins. Preliminary animal studies have found a significant drop in blood pressure following infusion of ß-endorphins. However, no hypotension was found if ß-endorphins were infused into animals pre-treated with pCPA, a specific depletor of serotonin (5-HT). Additionally, the hypotensive effect of the ß-endorphins was potentiated by fluoxetine, a specific serotonin re-uptake inhibitor (SSRI) (12). These results imply that ß-endorphins are a stimulus for 5-HT release that, in turn or in conjunction with the ß-endorphins may cause a decrease in sympathetic outflow.

Although the exact location of the central hypotensive effects of 5-HT remains unknown, it appears that it may be mediated by specific 5-HT1A receptors in the brain. Centrally administered 8-OH-DPAT, a 5-HT1A receptor agonist, has been shown to decrease blood pressure and sympathetic nerve activity (24). Conversely, exogenous 5-HT infused in the periphery has a number of effects including vasoconstriction.

5-HT has been shown to increase during exercise. These increases have been shown in brain tissue of rats (1) and in blood of humans (22). Interestingly, trained subjects have higher resting 5-HT levels than untrained subjects (20). Although there are no known studies that quantify both blood pressure and 5-HT levels with exercise, some inferences can be made. The majority of studies linking 5-HT with hypotension have been found with 5-HT levels manipulated in the brain. Peripheral 5-HT has been shown

to act on 5-HT2 receptors that cause vasoconstriction (23,19). This peripheral 5-HT is cleared rapidly via monoamine oxidase (5). Additionally, the sites of 5-HT release in the periphery are the gut and intestines (3). Both of these areas have minimal blood flow during exercise. Although it is debatable whether central 5-HT can cross the blood brain barrier, or if these increases are from platelet stores, if this system does play a role in blood pressure decrements, it is likely from central sources. Therefore, the purpose of this investigation was to examine the effects of central 5-HT on the magnitude of the blood pressure decrements after acute exercise. Central 5-HT levels were manipulated by treatment with an SSRI.

METHODS

Subjects

Eleven participants (9 males, 2 females), not actively involved in intense exercise programs and with borderline hypertension (145±15 / 72±10 mmHg) (mean±SD) volunteered to participate in this study. Mean age was 24.5±5.1 years; mean height 173.5±10.2 cm and a mean 77.5±8.9 kg. The McMaster University Human Ethics Committee approved the study and subjects were advised of the risks before providing written informed consent.

Preliminary Testing

Subjects' maximal aerobic power ($\dot{V}O_{2Peak}$) was assessed by a standard continuous progressive loading protocol on an electrically braked cycle ergometer (Eric Jaeger, Hoechberg, Germany). Expired gases were measured using a computerised open circuit gas collection and analysis system. Expired gases were collected and oxygen consumption was calculated every 30s during the test until fatigue. $\dot{V}O_{2Peak}$ was

determined as the highest oxygen consumption (averaged over 1 min) achieved during the test. Details of this testing have been previously described (16).

Protocol

Subjects reported to the laboratory after a four hour (h) fast on two separate occasions separated by at least fourteen days. For 11 days prior to each trial, in a randomised order, subjects ingested either placebo (sucrose) or an SSRI (Paroxetine HCl, 20mg·day^{-1}). During the latter 4 days preceding each trial, ingested food was kept constant between trials by having the subjects consume identical meals and portions. For the final 2 days subjects consumed pre-packaged diets free from any stimulants or depressants known to affect blood pressure (e.g. caffeine and alcohol) and void of any foods known to be high in tryptophan. Additionally, no formal exercise was performed during this period. Upon arriving at the laboratory, a 3.8 cm, 20 gauge catheter was inserted into the radial artery and coupled to a saline-Heparin (Wyeth-Ayerst, Toronto, Ontario) drip equipped with a pressure transducer (Novotrans, MX 800, Medex Inc., Hilliard, Ohio) for the direct measurement of blood pressure. This transducer was placed at mid-sternal level and coupled to an amplification system (Acudata, model 143, Honeywell Inc., Denver, Colorado) and an on-line data acquisition package (Windaq/200, DataQ Instruments Inc., Akron, Ohio) sampling at a frequency of 500 Hz. Calibration of the pressure monitoring system was completed using a mercury manometer before each trial. The system was calibrated to show a linear response between 0 and 300 mmHg. Subjects were also fitted with signal triggered ECG harness for recording of the QRS complex. Subjects then remained in a seated, resting position for a minimum of 30 min before the collection of baseline measurements. After a 5 min recording of baseline

blood pressure and HR, subjects completed 30 min of cycle ergometry at a power output eliciting 70% of $\dot{V}O_{2Peak}$. Blood pressure, HR and $\dot{V}O_2$ were monitored throughout, with 4 minute windows saved to disk at 15 and 30 minutes of exercise for later analysis. For trial 2, power output was kept consistent with trial 1.

After cycling, the participants remained quietly seated for 90 minutes. During this period, blood pressure and HR were continuously monitored with 4 minute windows saved to disk spanning 5, 10, 15, 30, 45, 60, 75 and 90 min post exercise (i.e. for the 5 min reading, blood pressure would be collected from min 3 to min 7). VO_2 was recorded subsequent to blood pressure recordings at 15, 30, 45, 60, 75 and 90 min post exercise. Additionally, arterial blood samples were drawn subsequent to blood pressure recordings at rest, 30 minutes of exercise and 5, 15, 30, 60 and 90 min post exercise for analysis of 5-HT, its major metabolite, 5-hydroxyindole acetic acid (5-HIAA), epinephrine and norepinephrine as outlined below. HR was recorded at three equidistant times during each segment and the average was taken as the HR for that segment. The two trials were performed at the same time each day and laboratory temperature and humidity was kept constant for each trial (22-24°C, 50% relative humidity).

5-HT And 5-HIAA Assay

Blood Collection

Blood was drawn into chilled plastic tubes containing Acid Citrate Dextrose (ACD) (25 g sodium citrate dihydrate, 14 g citric acid and 20 g dextrose / L). Additionally, since platelets are known to be the major source of 5-HT in the periphery, the 1L stock ACD solution also contained a cocktail of platelet activation inhibitors (containing 400 µL of 5 mg/mL prostaglandin E1, 400 µL of 25 mg/mL leupeptin, and 1 mL of 250 mM

phenylmethylsulfonyl fluoride mg/mL) known to arrest platelet activation. Blood was centrifuged at 800 rpm for 20 min. The platelet rich plasma was transferred to another chilled plastic tube and centrifuged at 2700 rpm for 9 min. Platelet poor plasma was removed and stored at -50°C for future analysis.

Sample Preparation

The plasma was thawed and duplicate 500 μL samples were alioquated into chilled plastic vials. Fifty μL of the internal standard, η-methyl serotonin (50 ng) was added. Protein was precipitated with 100 μL of ice cold 40% ($^{v}/_{v}$) percholoric acid and shaken for 10 min. Samples were spun at 4°C and 1000 g for 20 minutes and injected into the HPLC.

Apparatus

The HPLC system consisted of an injector pump (Waters 510, Waters Corporation, MA), an automated, refrigerated sample injector (Waters 712, Waters Corporation, MA), a reverse phase analytical column (Microsorb C_8, 4.6x10mm, Ranin, Corporation CA), protected by a guard column (Waters C_8, 2.9x20mm, Waters Corporation, MA) and an electrochemical detector (ESA Coulochem II, SPD, Ont.).

HPLC Conditions

The mobile phase consisted of acetonitrile (10%), sodium monobasic phosphate (6.9 g/L) heptane sulfonic acid (250 mg/L), and ethylenediaminetetraacetic acid (EDTA) (80 mg/L). The solution was adjusted to pH 3.2 with o-phosphoric acid and filtered through 4 μm membrane and degassed. The flow rate was set to 1.2 $mL \cdot min^{-1}$.

Epinephrine And Norepinephrine Assay

Blood Collection

Blood was drawn into chilled glass tubes containing ethylene glycol aminoethyl ether tetraacetic acid and reduced glutathione (Cat a Kit, Amersham Chemical, Ont.) and centrifuged at 4°C and 3000 rpm for 10 min. The plasma was transferred into chilled plastic tubes and stored at -50°C for future analysis.

Sample Preparation

Plasma was thawed and duplicate 1 mL samples were alioquated into chilled plastic vials. Ten μL of the internal standard, 3,4 dihydroxybenzylamine (DHBA) was added (9 ng), followed by 400 μL of Tris buffer (243.6 g Tris/L, 2 g EDTA/L, pH 8.8) and 10 mg alumina oxide. Samples were vortexed for 30 s and then shaken for 10 min. After centrifugation for 2 minutes, the supernatant was discarded. The alumina oxide was washed three times with 9x distilled water. Catecholamines were extracted from the alumina using 100 μL of .25N acetic acid and injected into the HPLC.

Apparatus

The HPLC system was as above, with the substitution of the reverse phase analytical column (Symmetry Shield RP_8, 3.9x150 mm, Waters Corporation, MA).

HPLC Conditions

The mobile phase consisted of methanol (3%), sodium monobasic phosphate (6.9 g/L) heptane sulfonic acid (250 mg/L), and EDTA (80 mg/L). The solution was adjusted to pH 3.6 with o-phosphoric acid and filtered through 4μm membrane and degassed. The flow rate was set to 1.5 $mL \cdot min^{-1}$.

Power Spectral Analysis of Heart Rate Variability (HRV)

To assess the potential contribution of the autonomic nervous system in PEH, power spectral analysis of HRV was employed. For a review on this procedure, the reader is referred to reference #10. Briefly, the time series of the HR data was linearly interpolated on an xy series to a standard interval series that can be numerically processed using standard fast fourier transformation (FFT) techniques. Data was then filtered using a lowpass Butterworth filter followed by a Hammond window. Power spectral density was calculated and then integrated and normalised. Data falling above 0.15 Hz was considered high frequency, and data falling below 0.15 Hz was considered low frequency. The low frequency area to high frequency area ratio was calculated and indicative of sympathetic activity. The high frequency to total area was calculated as a measure of parasympathetic activity.

Haemodynamic Analysis

Blood pressure waveforms were analysed using the Windaq data analysis program (DataQ Instruments Inc., Akron, OH). Systolic (SBP) and diastolic (DBP) blood pressure were calculated as the highest point and lowest point prior to the last inflection point in the waveform, respectively. The quotient of the integrated pressure and the duration of the time interval determined mean arterial pressure (MAP). Pulse pressure (PP) was taken as the difference between SBP and DBP. The rate pressure product (RPP) was calculated as product of the HR and the SBP divided by 1000.

Statistical Analysis

All data were analysed using one-way, repeated measures analyses of variance (ANOVA) (Statistica, Statsoft, OK). Significant findings were assessed using the Tukey

honestly significant difference post hoc comparison. All values are expressed as means ± SD unless otherwise noted.

RESULTS

Arterial blood pressure responses. The SSRI intervention was found to have no effect on any of the arterial blood pressure responses. As shown in fig. 1., there was a significant ($p<0.01$) increase in both SBP (145±15 to 185±19 mmHg) and DBP (72±10 to 79±10 mmHg) during the exercise. Thereafter, DBP returned to pre-exercise values for the duration of the 90 minute post exercise monitoring period. However, SBP was significantly decreased from baseline measurements during the initial 60 minutes following exercise. The nadir of the pressure decrement occurred 5 min after exercise (122±18 mmHg) and gradually increased towards baseline over the following 55 min, after which SBP had returned to normal.

Compared with pre-exercise, there was a significant ($p<0.01$) increase in MAP (92±12.0 to 107±11 mmHg) during exercise (fig.1). MAP decreased below baseline values during the initial 5 min following exercise (87±13 mmHg) and returned to normal for the remainder of the post exercise monitoring period.

Across trials, PP was significantly ($p<0.01$) increased during the exercise (73±9 to 106±17 mmHg). Post exercise PP was reduced from pre-exercise values for 75 minutes, after which it had returned to normal. The nadir of the PP decrement occurred 5 min after exercise (53±11 mmHg) and then gradually increased towards pre-exercise levels.

HR response. As expected, HR during the exercise bout increased significantly ($p<0.01$) above pre-exercise values (66±9 to 171±16 beats/min). Post exercise, HR steadily declined until baseline values were re-attained after 75 min.

Rate pressure product. As an indicator of myocardial oxygen demand and cardiac work, the rate pressure product (RPP) was significantly ($p<0.01$) increased during exercise from a resting measure of 9.5±1.4 to 30.9±4.2. The RPP steadily declined until pre-exercise values were re-established by 30 minutes after exercise.

Oxygen consumption. There was a minimal but significant ($p<0.05$) main effect for oxygen consumption. The SSRI trial resulted in an elevated $\dot{V}O_2$ as compared to the placebo trial (0.808±0.97 vs. 0.768±0.96 L/min). Additionally, across both trials, $\dot{V}O_2$ was significantly ($p<0.01$) elevated during exercise (0.245±0.06 to 2.575±0.35 L/min), but returned to pre-exercise levels by 15 min post exercise.

Catecholamines. As shown in fig. 2, the SSRI had no effect on catecholamine concentrations. Epinephrine was significantly ($p<0.01$) increased from baseline values during exercise (0.60±0.14 ng/mL to 1.3±1.6 ng/mL). Resting values were re-established by 5 min post exercise. Similarly, norepinephrine values were significantly ($p<0.01$) elevated with exercise (0.27±0.31 ng/mL to 4.58±2.1 ng/mL). Norepinephrine had returned to pre-exercise levels within 15 minutes of the cessation of exercise.

Indolamines. Peripheral measures indicated significant effects of the SSRI on indolamine levels (fig. 3). Plasma levels of 5-HT were significantly ($p<0.01$) attenuated across the SSRI trial as compared to the placebo trial (2.2±3.1 vs. 10.2±12.7 ng/mL).

Due to high variability, levels of plasma 5-HIAA failed to yield significant ($p>0.05$) differences, although values were augmented by ~13% during the SSRI intervention (539±269 vs. 471±303 ng/mL).

Power Spectral Analysis of HRV. HRV showed that the low frequency to high frequency area yielded (an indication of sympathetic activity) a significant increase at 10

and 15 minutes post exercise ($p<0.05$), after which it had returned to pre-exercise measures. The high frequency to total area (indicative of parasympathetic activity) was significantly ($p<0.01$) augmented at 5 minutes and attenuated at 15 minutes post exercise. All other time points did not differ from baseline values.

DISCUSSION

Our results indicate that, in borderline hypertensive participants, the serotonergic system does not influence the magnitude or duration of PEH. Given the significant decrease in peripheral 5-HT levels while under SSRI treatment and no change (and in fact a non-significant increase) in 5-HIAA, the major 5-HT metabolite, we are confident that brain 5-HT was elevated during and following exercise in the SSRI trial. This contradicts the findings of a previous study in rats (25), which suggested that PEH is influenced by the serotonergic system. In that study, however, exercise was simulated by stimulation of the sciatic nerve and thus differs from voluntary exercise. Other differences have been found between the rodent and human models investigating the existence, magnitude and potential mechanisms of PEH. For example, early work examining ß-endorphins and blood pressure, found that infusion of ß-endorphins resulted in a prolonged drop in blood pressure. In the rodent model, Hoffmann et al., (8) elegantly showed that binding of ß-endorphin to the κ, and to a lesser extent the δ-receptors, was responsible for PEH in rats. Human studies examining the contribution of the ß-endorphins to PEH have elicited contradictory results when blocking the opioid system with naloxone, an opioid receptor antagonist (2,7).

The concentrations of peripherally circulating 5-HT in the present study were considerably lower than those found in other studies (e.g. 22). We attribute this to our

control of platelet 5-HT release. Platelets are the primary storage vesicle for 5-HT in the periphery. It is known that clotting factors released at the arterial/venous puncture, as well as collection procedures can cause platelet release of 5-HT. Without the addition of platelet release inhibitors, as in the present study, it is likely that substantial increases in 5-HT will result from platelet release, and therefore not be indicative of 5-HT release from the brain and peripheral production sites (e.g. gut and intestine).

We have recently documented that there are no blood pressure changes resulting from 75 minutes of seated rest (16). We are therefore confident that the transient but significant decrements in blood pressure documented here are a result of the exercise interventions. Blood pressure, as in other studies from our laboratory (13,14,15,16) and elsewhere (11,21) tended to return towards baseline within the initial 60 to 90 minutes post exercise. Other studies have concluded that PEH may persist for up to 17 hours (e.g. 17, J. Hagberg, personal communication). The possibility exists that pronounced long duration blood pressure oscillations might occur post exercise. Although an early study by Pescatello et al. (17) does not report the blood pressure values tracked over the first hour post exercise, their subsequent measurements taken every 30 min for over 12 hours would suggest an oscillatory pattern of SBP.

An interesting and unexpected finding from the present study was the increased $\dot{V}O_2$ found under the SSRI condition. Simple t-tests indicated that no differences were observed between the pre-exercise placebo and SSRI conditions. Therefore, it can be concluded that an interaction had occurred between the drug intervention and exercise. Although not the purpose of this study, this may lend support to the central fatigue

hypothesis of exercise that suggests increases in brain serotonin promote the onset of fatigue.

Heart rate did not return to resting values until 75 min post exercise. This lengthy interval may be related to the fact that the subjects were untrained. Furthermore, it has been suggested that a borderline hypertensive population, as in the present study, may have an increased sympathetic outflow (4). This increased outflow, coupled with the (non-significant) traces of circulating catecholamines post exercise could also contribute to the increased heart rate post exercise. However, our finding that hypotension still occurred, despite the increased heart rate and elevated norepinephrine indicates the robustness of the PEH phenomenon.

It is interesting to note that the relative contribution of the SNS, as indicated by HRV, was increased during a portion of the PEH. Others who have measured HRV during PEH have found contradictory results (6,18). Similar to our results, Piepoli et al. (18) also found an increased SNS activity and attributed this to a compensatory, reflex mechanism to the observed hypotension.

The contradictory results found between mechanisms such as muscle sympathetic nerve activity, the opioid system as well as the vast differences seen between the existence, magnitude and response of PEH suggest that it is a phenomenon which is not controlled by a single factor. A complex matrix of blood pressure regulating factors including both central and peripheral mechanisms are likely responsible for PEH and require further investigation.

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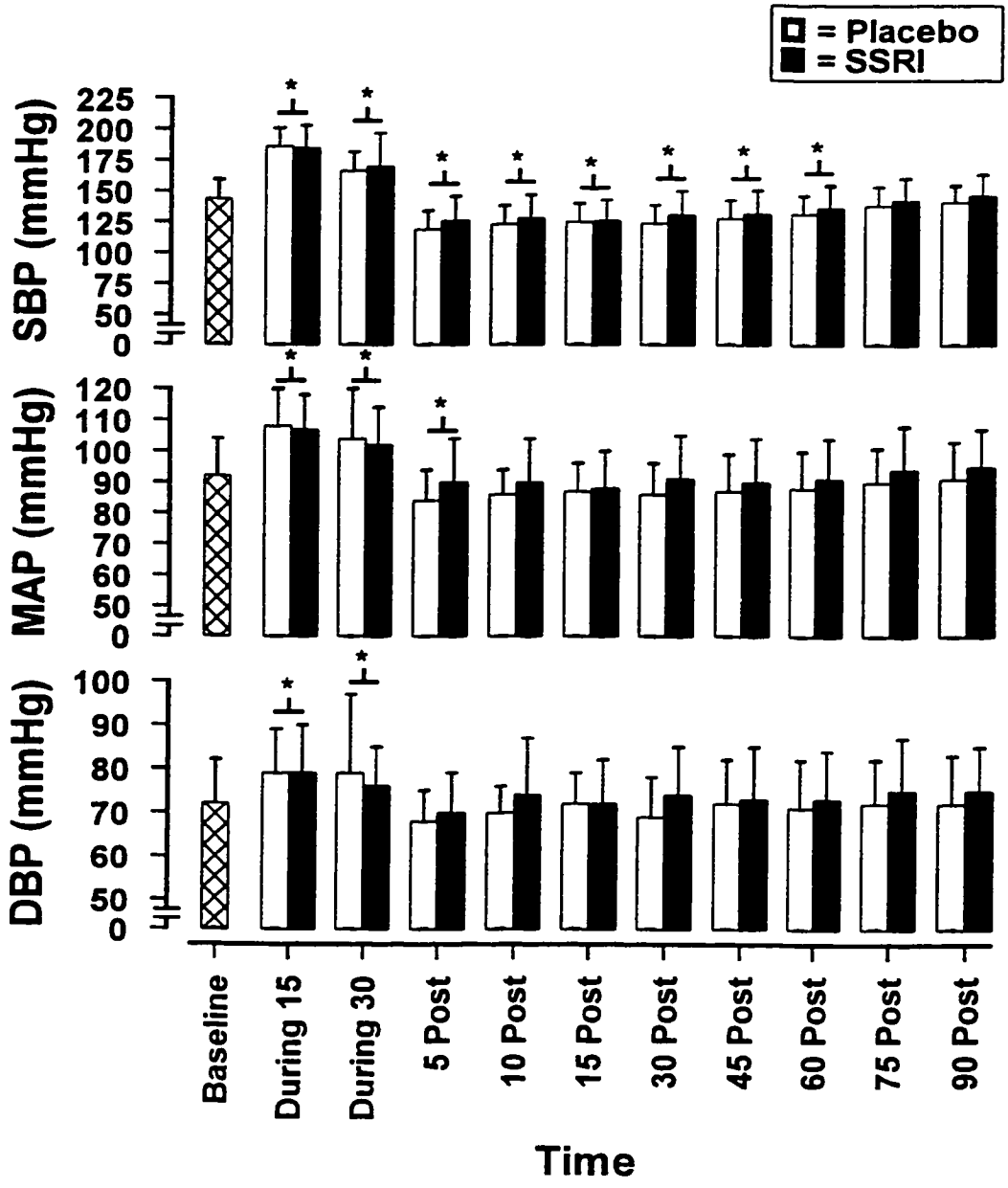
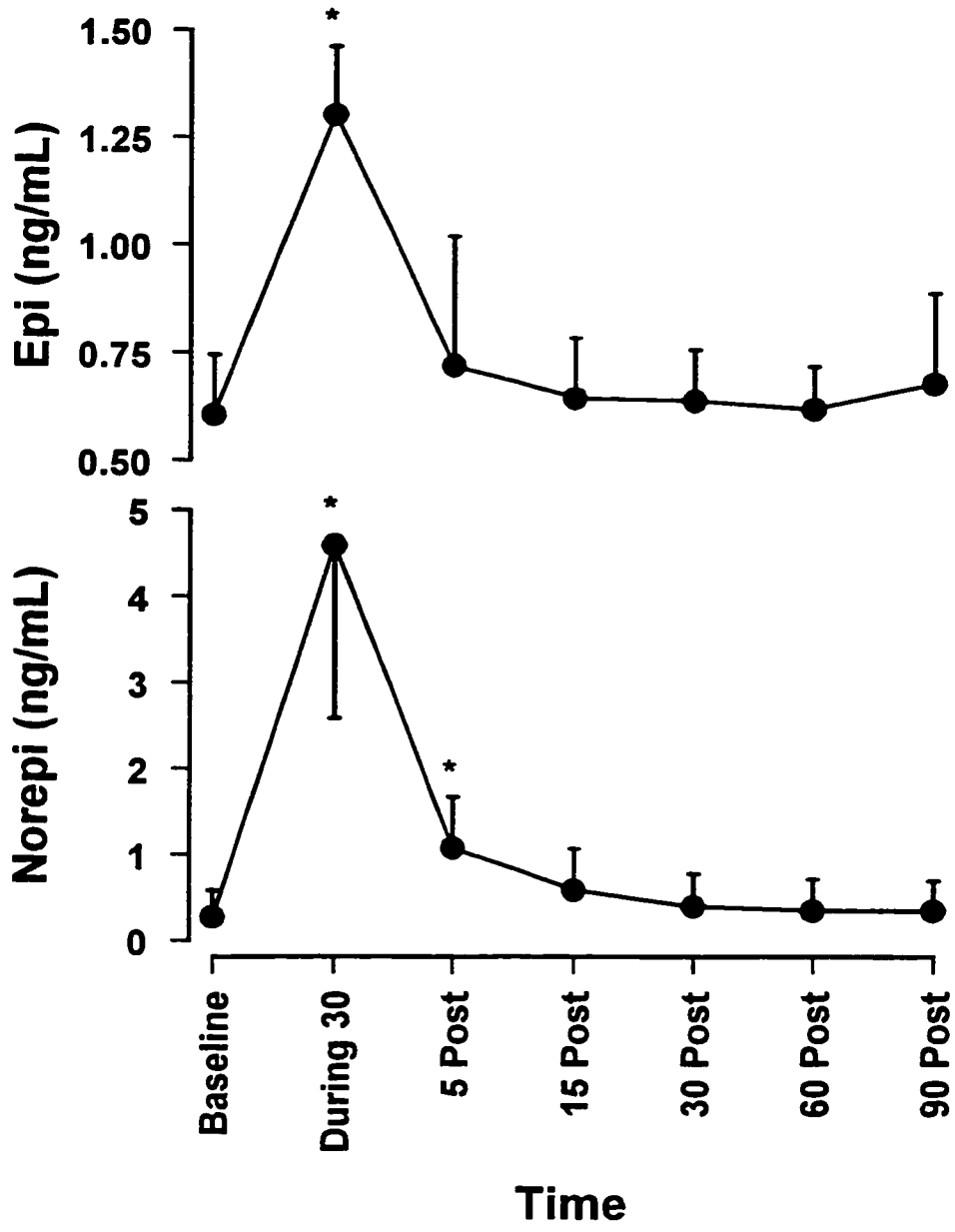
FIGURE CAPTIONS

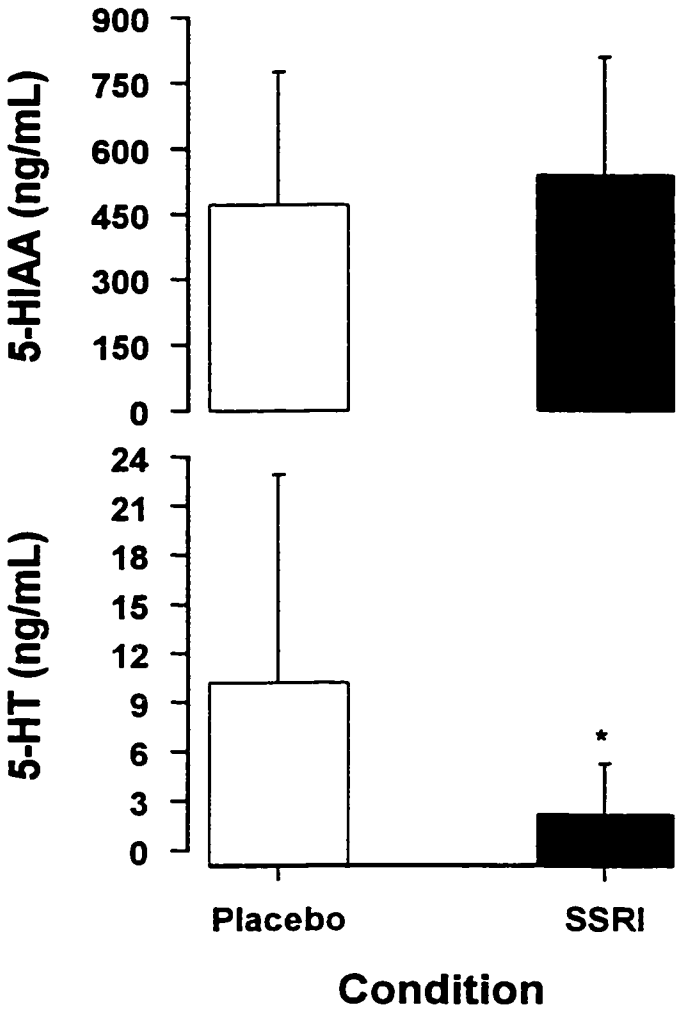
Figure 1. The effects of exercise on post exercise blood pressure. * indicates a significant difference from baseline. No differences were found between placebo and SSRI treatment.

Figure 2. The pooled effects of exercise on catecholamine levels. * indicates a significant difference from baseline. No differences were found between placebo and SSRI treatment.

Figure 3. The effects of SSRI treatment on peripheral measures of indolamine levels. * indicates a significant difference from placebo.


□ = Placebo
■ = SSRI
SBP (mmHg)
225
200
175
150
125
100
75
50
0
MAP (mmHg)
120
110
100
90
80
70
60
50
0
DBP (mmHg)
100
90
80
70
60
50
0
Baseline
During 15
During 30
5 Post
10 Post
15 Post
30 Post
45 Post
60 Post
75 Post
90 Post
Time


1.50
1.25
1.00
0.75
0.50
Epi (ng/mL)
*
5
4
3
2
1
0
Norepi (ng/mL)
*
*
Baseline
During 30
5 Post
15 Post
30 Post
60 Post
90 Post
Time


900
750
600
450
300
150
0
5-HIAA (ng/mL)
24
21
18
15
12
9
6
3
0
5-HT (ng/mL)
*
Placebo
SSRI
Condition

CHAPTER 8

Summary and Future Directions

8.1 SUMMARY

The purpose of the studies comprising this thesis was to provide a greater understanding of the nature of the exercise stimulus needed to elicit PEH and its possible causal mechanism(s). In this regard, its major scientific contribution may be that it has helped to eliminate a number of possible mechanisms and thus may serve as an important guide for future research.

Specifically, it is apparent that the magnitude of the PEH response does not depend upon exercise intensity, in that exercise at 50% $\dot{V}O_{2Peak}$ elicited the same response as exercise at 75% $\dot{V}O_{2Peak}$. Whether or not this conclusion would extend to even milder intensities (e.g. 30% $\dot{V}O_{2Peak}$) is not known. However, the practical significance of this finding is that an intensity of 50% $\dot{V}O_{2Peak}$ is easily attained by even an unfit and sedentary population as well as by seniors or obese individuals. Similarly, it appears that the duration of exercise necessary for eliciting PEH may be as brief as 10 minutes and that exercising for 15, 30 or 45 minutes has no further effect on the magnitude of this response. The magnitude of PEH is also unaffected by the size of the exercising muscle group as evidenced by data following arm and leg exercise at the same relative (but different absolute) intensity. In combination with the above findings regarding exercise intensity, this result suggests that the mechanism(s) causing PEH emanates from a central source rather than being due to a regional vasodilation in the previously exercised muscles. The decline in resting blood pressure that is induced by an acute bout of exercise is not confined to a condition of passive recovery, but also extends for at least 70 minutes of participation in mild exercise, as might be encountered in activities of normal daily living. Brief bouts of moderate intensity exercise, repeated

several times throughout the day, may thus be a potential strategy for the non-pharmacological treatment of hypertension. Finally, the involvement of the central serotonergic system as the mechanism causing PEH, is very unlikely and can probably be dismissed as a future area of inquiry.

8.2 FUTURE DIRECTIONS

For PEH to be used as a non-pharmacological treatment for hypertension, an accurate time course must be established for this effect. Although some authors have documented the persistence of PEH for up to 12 hours, previous contradictory findings, the inaccuracy of the measurement techniques and the failure to adequately control the conditions following the exercise period, leave questions as to the duration of PEH. Although, we have documented that significant decrements in blood pressure can persist for at least 70 min post exercise with no trend towards returning to baseline, the duration of the hypotension beyond this point is unclear. Future work needs to accurately establish the time course of PEH using precise measurement techniques and controlling the activity following exercise.

If PEH is to be used in the management of hypertension, there is a need to establish the interaction between exercise and various anti-hypertensive medications on PEH. Although mildly hypertensive individuals may be able to control their condition with exercise alone, more severely inflicted individuals may need to remain on medication. An early study by Wilcox et al. (1987) documented the additive effect of exercise and β-adrenergic antagonist drugs on post exercise hypotension. However, the constraints of β-adrenergic antagonist on exercise capacity may make this an unsuitable combination. The increasing popularity of other antihypertensive drugs such as calcium

channel blocking agents and inhibitors of angiotensin converting enzyme, which are more conducive to exercise, require investigation.

To gain a better understanding of blood pressure regulation, and the condition of hypertension, further insight is needed as to the mechanism(s) of PEH. The fact that exercise intensity, duration and active muscle mass do not influence the magnitude of the hypotensive response would suggest a central mechanism or a change in vascular sensitivity throughout the body. Recent work, as outlined in chapter two, suggests that vascular sensitivity may play a dominant role in PEH. Whether a potential change in vascular sensitivity is mediated by local factors or by central command needs to be addressed before the true role of vascular sensitivity in PEH is known.

Given the many factors regulating blood pressure, the interaction between such factors and the redundancies built in to the blood pressure control system, it may prove impossible to identify the single causal mechanism for PEH. However, future research in this area will advance our understanding of blood pressure regulation.

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APPENDIX A

Previously Published Material:
Hypotension Following Mild Bouts Of Resistance
Exercise And Submaximal Dynamic Exercise

Eur J Appl Physiol (1999) 79: 148–154

ORIGINAL ARTICLE

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Hypotension following mild bouts of resistance exercise and submaximal dynamic exercise

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Abstract Our purposes were (1) to examine resting arterial blood pressure following an acute bout of resistance exercise and submaximal dynamic exercise, (2) to examine the effects of these exercises on the plasma concentrations of atrial natriuretic peptide ([ANP]), and (3) to evaluate the potential relationship between [ANP] and post-exercise blood pressure. Thirteen males [24.3 ± (2.4) years] performed 15 min of unilateral leg press exercise (65% of their one-repetition maximum) and, 1 week later, ≈15 min of cycle ergometry (at 65% of their maximum oxygen consumption). Intra-arterial pressure was monitored during exercise and for 1 h post-exercise. Arterial blood was drawn at rest, during exercise and at intervals up to 60 min post-exercise for analysis of haematocrit and [αANP]. No differences occurred in blood pressure between trials, but significant decrements occurred following exercise in both trials. Systolic pressure was ≈20 mmHg lower than before exercise after 10 min, and mean pressure was ≈7 mmHg lower from 30 min onwards. Only slight (non-significant) elevations in [αANP] were detected immediately following exercise, with the concentrations declining to pre-exercise values by 5 min post-exercise. We conclude that post-exercise hypotension occurs following acute bouts of either resistance or submaximal dynamic exercise and, in this investigation, that this decreased blood pressure was not directly related to the release of αANP.

Key words Post-exercise hypotension · Intra-arterial pressure · Submaximal dynamic exercise · Resistance exercise

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Introduction

It has been estimated that one in five individuals suffer from hypertension (Joffres et al. 1992). Although it has been known for some time that chronic exercise training can result in lower resting blood pressure in hypertensive individuals (Tipton et al. 1991), more recent studies have indicated that even an acute bout of exercise may elicit transient decreases in blood pressure (e.g. Floras and Senn 1991; Floras and Wesche 1992). In individuals with essential hypertension such decrements may average 21 and 12 mmHg for systolic (SBP) and diastolic (DBP) pressure, respectively (Wilcox et al. 1982; Bennett et al. 1984; Pescatello et al. 1991; Floras and Wesche 1992), and may persist for as long as 12–17 h (Pescatello et al. 1991; J. Hagberg personal communication). Such findings suggest that acute bouts of exercise may have the potential to act as a beneficial, non-pharmacological aid in the treatment of hypertension. Although the majority of investigations have focused on endurance exercise as the stimulus for post-exercise hypotension (PEH; Wilcox et al. 1982; Bennett et al. 1984; Floras and Senn 1991; Pescatello et al. 1991; Floras and Wesche 1992), there is also evidence which suggests that resistance exercise yields similar results (Brown et al. 1994).

Unfortunately, studies examining PEH to date have used intermittent auscultatory methods to determine blood pressure. It is well known that respiration causes blood pressure to fluctuate due to changes in intrathoracic pressure. In addition, large fluctuations in blood pressure are evident approximately 2–5 times per minute. These fluctuations, sometimes known as Mayer waves, are of unknown origin. Given these shifts in blood pressure as well as the changes associated with exercise and movement, continuous beat-by-beat recording is needed to accurately detect the acute changes in blood pressure associated with PEH.

Atrial natriuretic peptide (ANP) is known to possess potent natriuretic and vasodilatory properties which

play an integrative role in fluid regulation and the control of blood pressure (deBold 1985). This hormone is released from the atrial granules in response to distension of the atria (Vollmar 1990) and has been shown to increase in the circulation in response to dynamic exercise (Perrault et al. 1991, 1994). Although the half life of ANP is quite short (2–3 min), it has been suggested that its haemodynamic effects persist for several hours (Espiner and Nicholls 1987). Several mechanisms may be responsible for its release during exercise, but it is generally accepted that these are secondary to the ANP release caused by the atrial distension imposed by increase in venous return (e.g. Ray et al. 1990). A number of studies have shown an increase in circulating concentrations of ANP ([ANP]) with endurance exercise (e.g. Perrault et al. 1991, 1994), suggesting that this response is due to the increased atrial distension associated with an enhanced venous return. Significant elevations of [ANP] have been found at peak exercise in the supine, compared to upright position (Ray et al. 1990; Bussieres-Chafe et al. 1994), yet, radionuclide ventriculography has demonstrated that the stroke volume augmentation that occurs in the supine position during cycle ergometry at power outputs above 25 W (including peak exercise) is negligible (Poliner et al. 1980; Steingart et al. 1984). This suggests that atrial distensions not the primary cause for ANP secretion in this instance. In addition we have observed increased circulating [ANP] in healthy young subjects in response to intensive heavy resistance exercise (MacDonald et al. 1995). Since such exercise results in marked elevations in blood pressure (MacDougall et al. 1985; Lentini et al. 1993; MacDougall 1994) but little or no change in end diastolic volume (Lentini et al. 1993), the mechanism for ANP release during weightlifting may involve factors other than atrial distension.

Although there is considerable descriptive literature on the occurrence of PEH, little is known about its underlying mechanism(s). Possibilities include decreased cardiac output (Hagberg et al. 1987) and/or peripheral resistance (Piepoli et al. 1993), increased circulating K^+ (Urata et al. 1987) and opioid-mediated decreases in sympathetic activity (Hoffman and Thoren 1988; Farrell et al. 1991). To our knowledge there have been no investigations of the possible causal relationship between exercise-released ANP and PEH.

This investigation had three purposes. The primary purpose was to evaluate the separate effects of submaximal cycling versus resistance exercise as modulators of PEH using the accuracy of intra-arterial blood pressure monitoring. A secondary purpose was to examine the stimulus for the secretion of αANP during exercise. It was hypothesised that by examining the ANP response to both cycle ergometry and heavy resistance exercise, it would be possible to uncouple the effects of a blood pressure, versus a volume load on the heart as a stimulus for ANP release. The third purpose of this study was to determine whether the occurrence of PEH is related to elevations in circulating [αANP].

Methods

Subjects

Thirteen recreationally active males aged [mean(SD)] 24.3(2.4) years, with a mean(SD) height of 175.9(5.0) cm and a mean (SD) body mass of 74.2(7.9) kg volunteered to participate in the study. After approval by the McMaster University Human Ethics Committee, subjects were advised of the risks associated with the study and provided written informed consent.

Preliminary testing

Prior to beginning the study, the subjects' maximum oxygen uptake ($\dot{V}O_{2max}$) was determined using an incremental cycle ergometry test to exhaustion. Using an electrically braked cycle ergometer (Eric Jaeger, Hoechberg, Germany), subjects pedalled at a cadence greater than 60 revolutions per minute (rpm). At the completion of each 2-min interval, the power output was increased by 20–60 W. Volitional exhaustion was deemed to be the point at which subjects could no longer maintain a pedal cadence of 60 rpm. Expired gases were collected using one-way air-flow valves (Hans Rudolph #2700, Hans Rudolph, Kansas City Mo, USA) and analysed on-line via an IBM-compatible computer using the TurboFit software package (Vacumetrics, Ven, Calif., USA) coupled with an AMETEK S3A I oxygen analyser (Applied Electrochemistry, Pittsburg, Pa, USA) and a Hewlett Packard 78356A carbon dioxide analyser (Hewlett packard, Mississauga, Ontario, Canada). Both analysers were calibrated prior to and following each test using gases of known oxygen (12.10%) and carbon dioxide (5.10%) content.

The mean $\dot{V}O_{2max}$ was found to be 53.9(7.4) ml · kg^{-1} · min^{-1}. For each individual, 65% of their $\dot{V}O_{2max}$ was calculated as the target oxygen consumption during the submaximal dynamic exercise trial. An average of 180(30) W was required to elicit 65% $\dot{V}O_{2max}$. Unilateral leg press strength was determined as the greatest weight that a subject could lift once with the dominant leg, through the entire range of movement (one-repetition maximum: 1RM). This resistance was determined using a progressive incremental protocol on a commercial leg press apparatus (Global Gym, model 3221-168, Global Gym Fitness Equipment, Weston, Ontario, Canada) with at least 3 min between attempts. The average 1RM weight subjects could lift was 111(15) kg. Sixty-five percent of each individual's value was termed the 65% 1 RM, and this value was used in the resistance exercise trial.

All subjects provided typical 4-day diet records (3 weekdays, 1 weekend day). From these, their average daily energy intake was calculated and pre-packaged diets were designed in order to control for caffeine and sodium intake. Since high protein ingestion has been shown to increase ANP secretion (Tam et al. 1990), subjects were asked to refrain from ingesting animal protein for 3 days prior to consumption of the pre-packaged diet. During the test day and the preceding day, subjects consumed the provided diet which contained approximately 75% carbohydrate, 20% fat and 5% protein and was low in sodium.

Experimental protocol

After a 7-h fast, the subjects reported to the laboratory and underwent auscultatory resting blood pressure measurement. Auscultatory readings averaged 130(13)·87(8) mmHg for SBP and DBP, respectively. A 3.8-cm, 20-gauge Angiocath (Becton Dickenson, Sandy, Utah, USA) was then inserted into either the brachial or radial artery (n = 10 brachial, n = 3 radial). The catheter was coupled to a saline-Heparin (Wyeth-Ayerst, Toronto, Ontario, Canada) drip equipped with a Novotrans pressure transducer (MX 800, Medex, Hilliard, Ohio, USA) for the direct measurement of blood pressure. This transducer was placed at mid-sternal level and coupled to an amplification system (Acudata, model 143, Honeywell, Denver, Colo., USA) and an on-line data acquisition package

(Windaq 200. DataQ Instruments. Akron. Ohio. USA). sampling at a frequency of 300 Hz. Calibration of the pressure-monitoring systems was completed using a mercury manometer prior to each trial. The intra-arterial catheter was calibrated to show a linear response between 0 and 300 mmHg. Reference electrodes. placed in the V5 positions. were affixed to a digital heart rate (HR) recorder which was coupled to a signal-triggered counting device (Lafayette Instrument. Model 54430. Lafayette. Ind.. USA) for the determination of summed cardiac cycles. Subjects remained in a seated resting position for a minimum of 20 min prior to the collection of baseline measurements.

The initial testing session required subjects to complete 15 min of unilateral leg press exercise at 65% of their predetermined 1RM. Timing of the lifting. lowering and lockout phases of the exercise was established using a metronome. The metronome emitted an audible stimulus at a frequency of 1 Hz. Subjects were asked to maintain a cadence of 2 during the lifting phase. 1 during the lockout and 3 during the lowering phase. in time with the metronome. During the session. subjects were free to alternate to the contralateral limb as fatigue occurred. At the cessation of exercise. subjects remained seated quietly for 1 h. for continued monitoring.

Intra-arterial blood pressure was monitored continuously throughout the session. with 30-s windows recorded at rest. 5. 10. and 15 min into exercise and then 1.5 3. 5. 10. 15. 30. 45 and 60 min post-exercise for subsequent analysis. Arterial blood was sampled approximately 15 s before and after each pressure-monitoring time point. Aliquots of blood were then mixed to approximate a single sample across each of the time points listed above. The blood was obtained from the arterial catheter site and collected in chilled collection vials which contained ethylenediaminetetraacetic acid (Vacutainer. Becton Dickenson. Rutherford. N.J.. USA). Capillary tubes were filled and subsequently centrifuged for haematocrit (Hct) determination in order to calculate possible shifts in plasma volume. Upon completion of the trial. the blood was centrifuged at 4°C and 3000 *g* for 30 min. Plasma was then extracted and stored at −50°C for later analysis.

The second testing session occurred 1 week later. with catheterisation. pressure. heart cycle monitoring and blood collection procedures being identical to the previous session. This trial required subjects to perform a bout of cycle ergometry at a power output which elicited 65% $\dot{V}O_{2max}$. Expired gases were collected to ensure that the target of 65% $\dot{V}O_{2max}$ was maintained. Collection times for pressures and blood samples in this trial were dependent upon the number of cardiac cycles recorded in the resistance exercise trial (e.g. if during the resistance exercise. blood pressure was taken at 5 min. at which point 800 cardiac cycles had occurred. during the cycle ergometry session pressure measurements would be collected at a time point corresponding to 800 cardiac cycles). This procedure was followed since ANP release is thought to be stimulated by the atrial distension caused by increased atrial filling during diastole. Since one would expect the total amount of ANP released to be a function of both the magnitude of the load and the duration over which it is imposed. summed cardiac cycles were held constant between the two trials in order to hold the number of occasions of diastolic filling constant. At the cessation of exercise. subjects remained quietly seated as in the initial trial.

To maintain consistency. samples were labelled corresponding to the resistance exercise trial with the following coding: BL. D5. D10. D15. 1:30P. 3P. 5P. 10P. 15P. 30P. 45P. 60P. where BL = baseline. D = during exercise. and P = post-exercise. and the number refers to the number of minutes during or post-exercise.

Analysis

Blood pressure waveforms were analysed using a Windaq data analysis program (DataQ Instruments). SBP and DBP were calculated as the highest point in the waveform and the lowest point in the waveform. respectively. Mean arterial pressure (MAP) was determined as the quotient of the integrated pressure and the duration of the time interval. The rate-pressure product (RPP) was calculated as the product of SBP and HR divided by 1000.

The plasma was analysed for human αANP using a commercially available human αANP [^{125}I] radioimmunoassay system (Amersham Chemicals, Oakville. Ontario. Canada). The intra-assay coefficient of variation was found to be ≈4.9%.

Subsequent testing

In order to assess the effects of 75 min of sitting on its own (e.g. without being preceded by exercise) on blood pressure. following the two sessions described above. two subjects returned to the laboratory for additional testing. Following arterial catheterisation. subjects remained seated in an identical manner to the previous two trials. Blood pressure and Hct were monitored as above for 75 min in order to determine the extent to which possible reductions in plasma volume due to a static seated position may have contributed to the response.

Statistical analysis

Each variable (as described above). with the exception of the subsequent non-exercise data for blood pressure and Hct influenced by the seated posture. were assessed using a single two-factor. repeated-measures analysis of variance (ANOVA) with trial (leg press and cycle ergometry) and time of measurement as the repeated measures. The subsequent non-exercise data were assessed using a single-factor. repeated-measures ANOVA with time (as above) as the repeated measure. The Tukey Honestly Significant Differences method was used to assess the location of any significant differences. A probability level of $P \leq 0.05$ was considered to be statistically significant. Unless otherwise stated. all values are expressed as the mean (SD).

Results

Matching the duration of the two exercise modes to total cardiac cycles resulted in a significantly different total exercise time [$F(1,12) = 20.69$. $P = 0.0007$] for cycling [(min:s) 13:47 (1:10)] compared to the resistance exercise (constant at 15:15).

Because of faulty preservative reagents, ANP analysis was confounded for seven subjects and it was therefore necessary to exclude these data. As shown in Fig. 1, in the remaining six subjects. no statistically significant differences in plasma [αANP] were found between the resistance and submaximal cycling trials [$F(1.5) = 1.11$, $P = 0.34$]. In addition plasma [αANP] failed to increase significantly with exercise [$F(11,55) = 1.05$. $P = 0.42$]. However. it should be noted that one subject (who exercised at the highest power output) did exhibit a more than five-fold rise in [αANP] during submaximal dynamic exercise.

Analysis of SBP (Fig. 2) produced a significant main effect [$F(11,132) = 101.74$. $P < 0.00001$] for time. indicating an increase in pressure at all time points during exercise as well as a reduction from baseline at the 10P, 15P. 30P. 45P and 60P time points. Collapsed across modality. maximal SBP was ≈225(31) mmHg and occurred during the initial 5 min of exercise. Conversely. the greatest decrement in SBP was evident at the 30P time point and was ≈20 mmHg below resting values. In addition. the SBP recorded 5 min into the submaximal dynamic exercise was significantly [$F(11,132) = 2.71$.

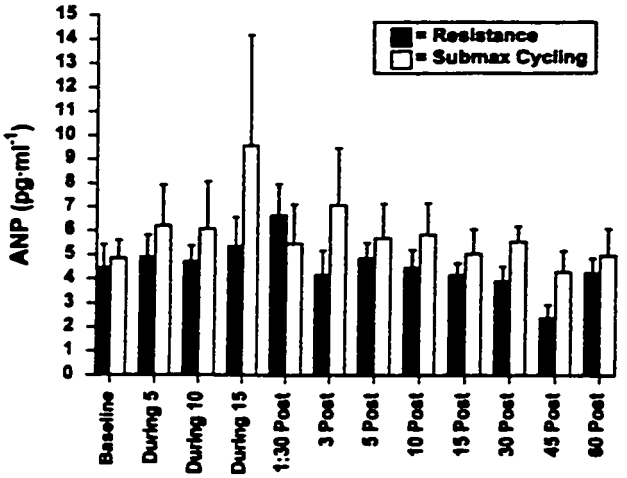

Fig. 1 The response of atrial natriuretic peptide *ANP*: [mean(SEM)] to resistance (*black bars*) and submaximal dynamic (*clear bars*) exercise (n = 6). The time scale on the abscissa is given as min (or min:s) during or post-exercise (*Post*)

$P < 0.00001$] elevated from the corresponding time point during the resistance trial.

Analysis of DBP (Fig. 2) indicated a significant main effect for time [$F(11,132) = 22.35$, $P < 0.00001$], but unlike SBP it did not decrease below baseline during recovery. Across trials, increases in DBP were found only during the exercise period, with maximal values reaching 93(15) mmHg at the D5 reading. The difference between exercise modalities failed to reach significance. Post hoc analysis of the significant [$F(11,132) = 10.02$, $P < 0.00001$] interaction did indicate that the average DBP that were incurred with resistance exercise were elevated above both the resting values and those reached during the cycle ergometry. Submaximal dynamic exercise failed to increase DBP.

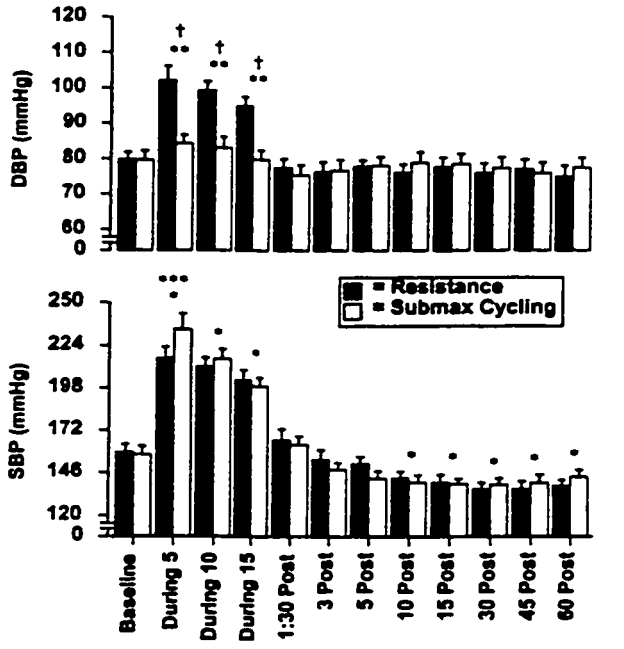

Fig. 2 The response of blood pressure [mean(SEM)] to resistance (*black bars*) and submaximal dynamic (*clear bars*) exercise *SBP* systolic blood pressure, *DBP* diastolic blood pressure pooled systolic data is significantly different from baseline: **systolic pressure of the resistance trial is significantly different from that of the submaximal cycling trial; ***pooled diastolic data is significantly different from baseline: †diastolic pressure of the resistance trial is significantly different from that of the submaximal cycling trial

MAP increased [F(11, 132) = 79.44, $P < 0.00001$] from 103(8) mmHg to a peak value of 127(13) mmHg during exercise (D5). The increases noted at the D10 and D15 time points were also significant. MAP was reduced at 30, 45 and 60 min post-exercise, with a maximal decrement of approximately 7 mmHg (at 45P) below baseline. Significant interactions [$F(11,132) = 8.72$, $P < 0.00001$] confirmed that resistance exercise elicited greater MAP increases than cycling exercise. During the 15 min of exercise, MAP averaged 129(12) mmHg during the resistance trial and 116(9) during the submaximal cycling trial.

Analysis of exercise oxygen consumption during exercise revealed both a main effect for trial [$F(1,12) = 73.50$, $P < 0.00001$] and time [$F(3,36) = 268.12$, $P < 0.00001$]. The trial effect was indicative of greater oxygen consumption during the submaximal cycling (which was ≈65% of $\dot{V}O_{2max}$). Submaximal cycling elicited an oxygen consumption of 35.2(6.8) versus 19.8(4.5) ml · kg^{-1} · min^{-1} for the resistance exercise. Post hoc analysis of time (irrespective of trial) revealed a significant increase from baseline to D5. This increase was further heightened at the D15 time point.

As shown in Fig. 3, changes in HR were consistent between conditions, both during and following exercise, with the exception of the D5 point where it was significantly [$F(11,132) = 4.91$, $P < 0.00001$] higher during the submaximal cycling trial. Resting HR was 69(12) beats per minute (bpm). This value increased significantly [$F(11,132) = 271.69$, $P < 0.00001$] with exercise at the D5 time point [131(15) bpm] and increased further to 152(16) bpm immediately prior to the cessation of exercise. In recovery, this value immediately dropped below exercise values, yet remained significantly elevated above baseline values for ≈15 min.

Analysis of RPP indicated that there was no main effect for trial. The RPP was significantly elevated from baseline at all points during exercise [$F(11,132) = 220.20$, $P < 0.00001$] and returned to resting values by approximately 3 min post-exercise (collapsed across trial). Results of the interaction [$F(11,132) = 7.20$, $P < 0.00001$] indicated that the RPP of the initial two time points during exercise (i.e. D5 and D10) were significantly greater during the resistance exercise session.

A main effect for trial indicated a significantly increased [$F(11,121) = 24.65$, $P < 0.00004$] Hct during the resistance exercise (Fig. 4). There was an additional main effect for time [$F(11,121) = 23.72$, $P < 0.00001$].

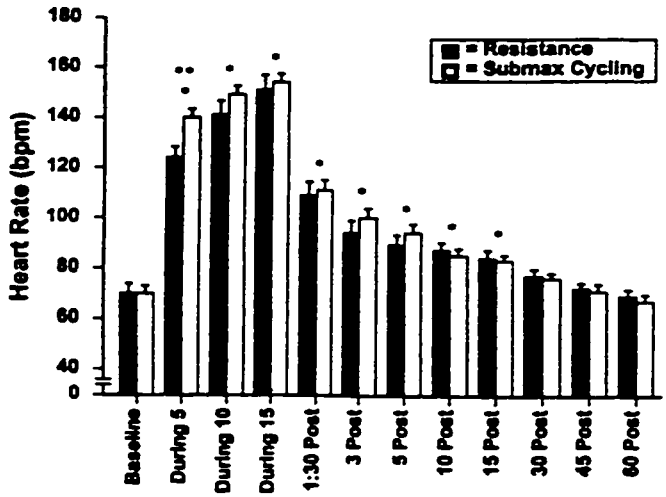

Fig. 3 The response of heart rate [mean(SEM)] to resistance (*black bars*) and submaximal dynamic (*clear bars*) exercise. *pooled data is significantly different from baseline. **data of resistance trial is significantly different from that of the submaximal cycling trial

indicating that Hct was significantly elevated from the onset of exercise until the 5P time point. There was a continued decrement after 5P, but it failed to reach significance. The significant interaction [$F(11,121) = 2.40$, $P = 0.01$] is indicative of Hct being higher in the resistance trial than in the submaximal cycling trial at D10, D15, 1:30P, 3P and 5P.

There were no observed changes for any blood pressure or Hct measures in the two individuals who were tested during the non-exercise condition.

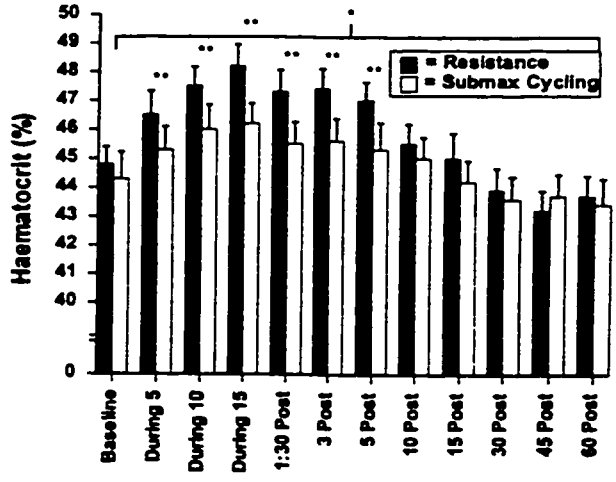

Fig. 4 The response of haematocrit [mean(SEM)] to resistance (*black bars*) and submaximal dynamic (*clear bars*) exercise. (*main effect for trial. **pooled data is significantly different from baseline

Discussion

The data indicate that when healthy young normotensive subjects perform ≈15 min of mild-intensity (65% $\dot{V}O_{2max}$) cycle ergometry or continuous weightlifting (65% 1RM) exercise, no changes occur in circulating [ANP]. Ten minutes following exercise, SBP decreased significantly below baseline, and 30 min following exercise MAP was also significantly lower than baseline. This post-exercise "hypotensive effect" was similar for both exercise modalities until measurements were terminated at 60 min. Follow-up studies using the identical methodology in a sub-sample of subjects who simply remained in the same seated position (without performing exercise), revealed no changes in resting blood pressure (Table 1), thus indicating that the observed hypotensive response was due to the exercise intervention.

Considerable intra- and intersubject variability was evident in the αANP response to exercise. The 89% increase in [αANP] at the 15-min point of the cycle ergometry exercise was largely due to the exaggerated response of one subject and was not statistically significant. Similarly, the 49% elevation in [αANP] at (min:s) 1:30 following the resistance exercise, the result taken from six subjects, was not statistically significant. Lentini et al. (1993) previously found pronounced ventricular dimension changes with resistance and submaximal dynamic exercise. A sub-sample of subjects in the current study underwent echocardiography to confirm these volume changes in the right atrium. The volume of the right atrium was found to be statistically significantly augmented during the submaximal cycling trial and statistically significantly reduced during the resistance trial. The failure to detect an increase in αANP release with either form of exercise was unexpected, in light of these changes in cardiac volumes and the heightened blood pressures associated with the resistance exercise. It is possible that the duration of exercise was insufficient to elicit αANP release during the submaximal cycling trial. In addition, blood pressure did not increase as much in this study as in our previous study where a significant release of αANP was observed with resistance exercise (MacDonald et al. 1995).

The significant increase in Hct which was detected during the resistance exercise, and which persisted until 5 min following exercise, has been well documented (Goodman et al. 1993; Ploutz-Snyder et al. 1995). Loss of plasma to the extravascular space in muscle is thought to be caused by the increased hydrostatic capillary pressures that accompany the dramatic increases in blood pressure which occur with each lift (MacDougall et al. 1985; Ploutz-Snyder et al. 1995). Haemoconcentration is also known to occur with endurance exercise, but the magnitude is considerably less (Novosadova 1977). The finding that Hct returned to normal after 5 min of recovery indicates that shifts in plasma volume were only transient and thus could not have been the cause for the PEH which occurred.

Table 1 Data from subsequent non-exercise trials. The time points are labelled to correspond to the exercise trials, although no exercise occurred. (*During* During exercise, *Post* post-exercise)

Subject	Baseline	During 5	During 10	During 15	1:30 Post	3 Post	5 Post	10 Post	15 Post	30 Post	45 Post	60 Post
					Haematocrit (%)							
1	47	48	44	46	45	46	46	46	46	48	44	46
4	41	42	42	41	41	42	41	42	41	42	41	42
					Mean blood pressure (mmHg)							
1	91	94	92	92	96	96	94	93	92	88	88	88
4	88	95	92	90	92	89	91	90	85	91	96	93

PEH has been documented to occur to a greater extent in hypertensive subjects than in normotensive subjects. In addition, many investigations of PEH in normotensive subjects have yielded contradictory results (Floras and Senn 1991; Pescatello et al. 1991; Floras and Wesche 1992; Hara and Floras 1992). In previous studies, however, blood pressure was measured by indirect methods that may have contributed to these discrepancies. In addition, no standardised body posture has been accepted for the post-exercise measurement period. In the present study, decrements in average SBP that were observed following exercise exceed those normally reported for a normotensive population. This may be partially because in the present study intra-arterial pressure was monitored directly. This method of sampling is more apt to detect small differences in pressure and is less affected by motion and limb position than the auscultatory methods used in the majority of studies (Kiyonaga et al. 1985; Landry et al. 1992). Unlike a number of previous reports, the average DBP observed following exercise in the present study did not parallel the change in systolic pressure (e.g. Wilcox et al. 1982; Bennett et al. 1984; Kaufman et al. 1987; Hara and Floras 1992). A possible explanation for this may be that some studies which report a decrease in DBP following exercise involved measurement of subjects in the supine position (Piepoli et al. 1993), whereas the present study maintained subjects in the sitting position. Bennett et al. (1984) suggested that the decreases in DBP which are detected post-exercise differ by approximately 6 mmHg between the sitting and standing position, with the greatest reductions occurring in the sitting position. It is possible that similar differences exist between the sitting and supine position, and thus, changes in DBP might not be detected in seated, normotensive subjects.

With the exception of maximal exercise tests (which generally last ≈8–12 min), the majority of endurance exercise protocols which have resulted in PEH have ranged from 20 to 60 min in duration (Bennett et al. 1984; Floras and Senn 1991; Floras and Wesche 1992; Hara and Floras 1992). The exercise intensities used in those studies were ≈75% of maximal HR. Assuming that subjects in the present study exercised at 65% $\dot{V}O_{2max}$ for approximately 13.5 min, this study has documented the occurrence of PEH after a mild bout of exercise of shorter duration than has been previously reported. This may have significant clinical implications, since this is a readily obtainable target intensity and duration, even for the hypertensive and elderly population.

The present study has also documented the occurrence of PEH after a bout of resistance exercise. Previous work in this area is sparse and contradictory. Brown et al. (1994) observed decreases in blood pressure after a bout of resistance exercise, whereas O'Connor et al. (1993) reported elevations in blood pressure following resistance exercise. The present study confirms that PEH occurs in response to resistance exercise. Moreover, the significantly decreased SBP and MAP values recorded at the termination of measurement (after 1 h) in the rest phase concur with reports of prolonged hypotension (Pescatello et al. 1991; J. Hagberg, personal communication).

In the present study, αANP appears not be a significant modulator of PEH since both the resistance and submaximal dynamic exercise modalities had a minimal effect on circulating levels of αANP. Moreover, any changes in [ANP] had disappeared following 5 min of recovery, and significant declines in MAP did not occur until 30 min following the cessation of exercise. This is in agreement with previous research (Perrault et al. 1991; Bussieres-Chafe et al. 1994; Perrault et al. 1994) which has found a return to baseline [ANP] by 30 min following upright exercise. However, the possibility of a delayed effect of ANP on the cardiovascular control centres modulated by the earlier ANP release cannot be discounted, nor can the potential contribution of ANP to PEH during longer, more intense bouts of exercise.

Although the catheter provided a saline drip, the volume infused over the testing session was minimal [62.3(30.2) ml], and is similar to that of the blood withdrawn for analysis (≈72 ml). This would therefore argue against a hypotensive effect due to decreased total blood volume.

Finally, the fact that Hct did not change during the 75 min non-exercise control trial (Table 1), nor during the recovery portion of the exercise trials in which PEH occurred, argues against vascular pooling as a causal mechanism. One might postulate that maintaining a relatively static body position for 60 min caused a shift of plasma from the vascular space and thus a decreased the total blood volume resulting in a subsequent drop in blood pressure. It is apparent that this possibility can also be dismissed as a mechanism.

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APPENDIX B

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APPENDIX C

Statistical Summaries

Manuscript #1 – The effects of exercise intensity on post exercise hypotension

Systolic Blood Pressure

Summary of all Effects; design: (sbp.sta)
1-TRIAL, 2-TIMEPOI

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	194.4643	9	1058.829	.183660	.678321
2	6	280.7310	54	98.892	2.838754	**.017815**
12	6	90.8310	54	93.140	.975204	.450961

Diastolic Blood Pressure

Summary of all Effects; design: (dbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	.57857 9	2	96.8008	.001949	.965748
2	6	92.22857	54	33.4243	2.759324	**.020591**
12	6	51.02857	54	51.0286	1.000000	.434960

Mean Arterial Pressure

Summary of all Effects; design: (map.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	74.3143	9	391.4730	.189832	.673319
2	6	127.0952	54	37.2937	3.407959	**.006339**
12	6	48.8476	54	54.4323	.897402	.503609

Manuscript #2a – The effects of 15, 30 and 45 minutes of exercise duration on post exercise hypotension.

Systolic Pressure

Summary of all Effects; design: (sbp.sta)
1-TRIAL, 2-TIME POINT

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	2	171.7619	24	270.5873	.634774	.538722
2	6	608.8193	72	65.4013	9.308978	**.000000**
12	12	63.8046	144	47.0097	1.357266	.193216

Diastolic Pressure

Summary of all Effects; design: (dbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	2	84.6803	22	217.9817	.388474	.682651
2	6	228.1228	66	37.7828	6.037737	**.000045**
12	12	23.4986	132	33.0154	.711746	.737894

Mean Pressure

Summary of all Effects; design: (map.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	2	7.1648	24	208.5577	.03435	.966277
2	6	402.0891	72	36.0852	11.14278	**.000000**
12	12	26.1477	144	35.7489	.73143	.718891

Heart Rate

Summary of all Effects; design: (hr.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	2	962.819	24	208.9793	4.60725	**.020258**
2	6	3782.665	72	52.4857	72.07037	**.000000**
12	12	54.821	144	23.8713	2.29653	**.010486**

VO2

Summary of all Effects; design: (vo2l.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	2	.026093	24	.008852	2.94756	.071669
2	6	.123108	72	.005975	20.60352	**.000000**
12	12	.002521	144	.002693	.93619	.512884

Haematocrit

NOTE: N=10, analysed on 45 minute trial only

Summary of all Effects; design: (hct.sta)
1-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	9	13.83970	81	1.233641	11.21858	**.000000**

Manuscript #2b – The effects of 10 and, 30 minutes of exercise duration on post exercise hypotension.

SBP

Summary of all Effects; design: (sbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	1605.143	7	527.0816	3.045340	.124481
2	6	322.842	42	64.4987	5.005405	**.000600**
12	6	97.747	42	51.9953	1.879920	.106929

DBP

Summary of all Effects; design: (dbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	540.3214	7	583.8112	.925507	.368079
2	6	120.0714	42	43.4728	2.761991	**.023559**
12	6	31.4881	42	31.5017	.999568	.438368

MAP

Summary of all Effects; design: (dbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	830.5804	7	601.3559	1.381179	.278322
2	6	161.1607	42	48.1335	3.348202	**.008704**
12	6	52.3512	42	36.9362	1.417340	.230752

VO_2

Summary of all Effects; design: (vo2.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	.003913	7	.018582	.21057	.660227
2	6	.025974	42	.001605	16.18659	**.000000**
12	6	.000998	42	.000696	1.43402	.224614

Heart Rate

Summary of all Effects; design: (hr.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	160.321	7	124.9541	1.28304	.294637
2	6	1233.717	42	18.7241	65.88940	**.000000**
12	6	30.759	42	12.3916	2.48224	.038086

Manuscript #3 – The central versus peripheral control of post exercise hypotension by comparison of active muscle mass.

SBP

Summary of all Effects; design: (sbp - delta.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	224.0000	8	521.6607	.429398	.530672
2	6	582.8889	48	103.2907	5.643190	**.000170**
12	6	74.4444	48	41.0010	1.815674	.115904

DBP

Summary of all Effects; design: (dbp - delta.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	97.7857	8	302.4464	.323316	.585225
2	6	151.7302	48	46.1944	3.284598	**.008675**
12	6	27.6190	48	31.1131	.887698	.511339

MAP

Summary of all Effects; design: (dbp - delta.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	9.1746 8	41	4.5496	.022131	.885419
2	6	223.7169	48	60.4223	3.702556	**.004191**
12	6	43.6005	48	34.9547	1.247344	.299452

Manuscript #4 – The central versus peripheral control of post exercise hypotension by comparison of active muscle mass.

SBP

Summary of all Effects; design: (sbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
Time	1	7854.006	7	695.8063	11.28763	**.012089**
Trial	9	3478.542	63	67.1424	51.80846	**.000000**
12	9	333.826	63	34.7686	9.60137	**.000000**

DBP

Summary of all Effects; design: (dbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	828.1000	7	178.5571	4.637731	.068256
2	9	110.3861	63	24.2147	4.558644	**.000121**
12	9	26.5306	63	8.3845	3.164229	**.003268**

MAP

Summary of all Effects; design: (map.sta)
1-TIME, 2-TRIAL

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	2379.306	7	185.9348	12.79645	**.009010**
2	9	428.992	63	25.2051	17.02009	**.000000**
12	9	67.487	63	12.5439	5.38003	**.000019**

Heart Rate

Summary of all Effects; design: (hr.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	12285.03	7	261.5822	46.9643	**.000241**
2	9	5605.73	63	50.0345	112.0371	**.000000**
12	9	780.37	63	17.3103	45.0813	**.000000**

Manuscript #5 – Post Exercise Hypotension Is Not Mediated by the Serotonergic System in Borderline Hypertensive Individuals.

SBP

Summary of all Effects; design: (sbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	1356.731	10	678.2042	2.00048	.187622
2	10	8662.968	100	143.3860	60.41713	**.000000**
12	10	45.750	100	94.1423	.48596	.895644

DBP

Summary of all Effects; design: (dbp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	228.2025	10	284.7298	.801470	.391694
2	10	179.9116	100	56.2834	3.196531	**.001337**
12	10	20.6388	100	25.9361	.795757	.632922

MAP

Summary of all Effects; design: (map.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	544.5000	10	365.5182	1.48967	.250267
2	10	974.3480	100	64.6907	15.06165	**.000000**
12	10	38.0273	100	24.2355	1.56908	.126851

Pulse Pressure

Summary of all Effects; design: (pp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	472.083	10	334.2736	1.41226	.262137
2	10	6475.956	100	76.8736	84.24165	**.000000**
12	10	23.683	100	69.5136	.34069	.967689

Rate Pressure Product

Summary of all Effects; design: (rpp.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	3.910	10	10.39250	.3763	.553309
2	10	1342.009	100	6.23120215	.3691	**.000000**
12	10	.616	100	2.89601	.2129	.994668

Heart Rate

Summary of all Effects; design: (hr.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	56.24	10	177.0624	.3177	.585438
2	10	30591.91	100	115.0795	265.8328	**.000000**
12	10	15.64	100	54.7877	.2854	.983130

VO_2

Summary of all Effects; design: (vo2.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	.07935	10	.015183	5.2266	**.045308**
2	8	22.19895	80	.038970	569.6411	**.000000**
12	8	.00183	80	.004157	.4406	.893110

EPI

Summary of all Effects; design: (epi.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	.282392	10	.633681	.445637	.519522
2	6	1.386880	60	.428671	3.235299	**.008049**
12	6	.174708	60	.257804	.677678	.668120

Nor Epi

Summary of all Effects; design: (norepi.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	.05777	10	.366116	.15778	.699554
2	6	54.10034	60	.927467	58.33127	**.000000**
12	6	.01236	60	.236532	.05227	.999377

Serotonin

Summary of all Effects; design: (5ht.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	2484.018	10	313.2484	7.929866	**.018286**
2	6	18.612	60	58.1020	.320326	.923877
12	6	18.858	60	61.5363	.306454	.931199

5 Hydroxy Indole Acetic Acid

Summary of all Effects; design: (5-hiaa.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	176905.4	10	224602.0	.787639	.395659
2	6	50071.4	60	52505.2	.953647	.464217
12	6	40591.9	60	50196.5	.808659	.567282

LF:HF Ratio

Summary of all Effects; design: (lfhf ratio.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	.06657	10	23.04737	.002889	.958196
2	8	47.60390	80	17.52923	2.715687	**.010646**
12	8	20.33316	80	18.81334	1.080785	.385086

HF to Total Ratio

Summary of all Effects; design: (hf to total.sta)
1-TRIAL, 2-TIME

	df Effect	MS Effect	df Error	MS Error	F	p-level
1	1	.001120	10	.031363	.035701	.853913
2	8	.055090	80	.017291	3.186117	**.003457**
12	8	.015985	80	.018603	.859270	.554225

APPENDIX D

Sample Consent Forms

McMaster University

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Fax 905.523.6011
http://www.kinlabserver.mcmaster.ca

Post Exercise Hypotension

Consent Form

INVESTIGATORS	ADDRESSES	EXTENSION
Dr. J.D. MacDougall	Dept. of Kinesiology	x24647
Mr. J.R. MacDonald	Dept. of Kinesiology	x23016
Mr. C. Hogben	Dept. of Kinesiology	

Purpose

Recent literature has indicated that there is a decrease in blood pressure following an acute bout of exercise. The magnitude and duration of this decrement has yet to be definitively determined. There is also a lack of information as to the exercise stimulus, which elicits this phenomenon. The purpose of this study is to determine if the post exercise hypotension is dependent on the intensity of exercise.

Procedure

A) Preliminary Testing

Participants will be required to perform a maximal oxygen uptake test on a cycle ergometer in order to determine their percent of maximum values for the testing workloads. Resting blood pressure will also be measured five (5) times using a non-invasive finger blood pressure cuff.

B) Testing Protocol

Participants will be required to report to the laboratory on two separate occasions for testing. Each session will require participants to undergo a weight assessment. Subsequent to this, resting blood pressure measurements will be made. Participants will then exercise at 50 or 70% of their maximum level for 30 minutes (random order). Blood pressure, oxygen consumption and haematocrit will be determined at each 15 minutes of exercise. Following this, participants will remain quietly seated and similar measurements will be recorded at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post exercise.

Potential Risks

Exercise may cause slight muscle strains and, as with all exercise, there is a slight risk of having a heart attack or collapsing. A supervised, adequate warm-up period should alleviate the complication of muscle strains. Haematocrit measurements will require blood samples to be taken from the finger tip. This has been found to be slightly uncomfortable to some participants. There is also a very minimal risk of infection at the puncture site, which could, in theory result in a generalised infection of the body. This complication has never been documented in our laboratory. A physician will be made available in the event that complications do arise.

Withdrawal

Participants will be free to withdrawal at any point during the study without repercussion. Withdrawing participants will be permitted to view their collected data to date, after which point the data will be destroyed.

Confidentiality

The data will be stored inside a locked filing cabinet within a locked office located in the Ivor Wynne Centre. Only the listed investigators will have access to this data. Collected data will be used in the preparation of scientific manuscripts. Participants will in no way be identified in resulting publications or presentations.

Remuneration

Participants will be compensated $50.00 for their time commitment to this study

Having read the above information, I consent to participate in all aspects of the study. I am aware that I am able to withdrawal at any time without repercussion.

Signature_____ Date_____

Witness_____ Date_____

McMaster University

Department of Kinesiology 1280 Main Street West Hamilton, Ontario, Canada L8S 4K1 Phone 905.525.9140 Fax 905.523.6011 http://www.kinlabserver.mcmaster.ca

Post Exercise Hypotension

Consent Form

INVESTIGATORS	ADDRESSES	EXTENSION
Dr. J.D. MacDougall	Dept. of Kinesiology	x24647
Mr. J.R. MacDonald	Dept. of Kinesiology	x23016
Mr. C. Hogben	Dept. of Kinesiology	
Mr. N. Fox	Dept. of Kinesiology	

Purpose

Recent literature has indicated that there is a decrease in blood pressure following an acute bout of exercise. The magnitude and duration of this decrement has yet to be definitively determined. There is also a lack of information as to the exercise stimulus, which elicits this phenomenon. The purpose of this study is to determine if the post exercise hypotension is dependent on the duration of exercise.

Procedure

A) Preliminary Testing

Participants will be required to perform a maximal oxygen uptake test on a cycle ergometer in order to determine their percent of maximum values for the testing workloads. Resting blood pressure will also be measured five (5) times using a non-invasive finger blood pressure cuff.

B) Testing Protocol

Participants will be required to report to the laboratory on three separate occasions for testing. Each session will require participants to undergo nude weight assessment. Subsequent to this, resting blood pressure measurements will be made. Participants will then exercise for a duration of 15, 30 or 45 minutes (random order). Blood pressure, oxygen consumption and haematocrit will be determined at each 15 minutes of exercise. Following this, participants will remain quietly seated and similar measurements will be recorded at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post exercise.

Potential Risks

Exercise may cause slight muscle strains and, as with all exercise, there is a slight risk of having a heart attack or collapsing. A supervised, adequate warm-up period should alleviate the complication of muscle strains. Haematocrit measurements will require blood samples to be taken from the finger tip. This has been found to be slightly uncomfortable to some participants. There is also a very minimal risk of infection at the puncture site, which could, in theory result in a generalised infection of the body. This complication has never been documented in our laboratory. A physician will be made available in the event that complications do arise.

Withdrawal

Participants will be free to withdrawal at any point during the study without repercussion. Withdrawing participants will be permitted to view their collected data to date, after which point the data will be destroyed.

Confidentiality

The data will be stored inside a locked filing cabinet within a locked office located in the Ivor Wynne Centre. Only the listed investigators will have access to this data. Collected data will be used in the preparation of scientific manuscripts. Participants will in no way be identified in resulting publications or presentations.

Remuneration

Participants will be compensated $50.00 for their time commitment to this study

Having read the above information, I consent to participate in all aspects of the study. I am aware that I am able to withdrawal at any time without repercussion.

Signature_____ Date_____

Witness_____ Date_____

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CONSENT FORM

The effects of exercise duration on post exercise blood pressure and muscle sympathetic nerve activity

INVESTIGATORS	ADDRESSES	TELEPHONE
Dr. J.D. MacDougall	Dept. of Kinesiology	x24647
Dr. S.M. Ettinger	Penn State Univ.	(717) 531-8407
Mr. J.R. MacDonald	Dept. of Kinesiology	x23016

Purpose:

Recent evidence has suggested that acute bouts of endurance exercise can cause an attenuation of post exercise blood pressure. These investigations will determine if this decrement in pressure is affected by a) the intensity of exercise and/or b) sympathetic neuronal activity which is known to mediate the dilation of the blood vessels.

Procedure:

Session 1 - Maximal Oxygen Consumption

During the first testing session, you will undergo a cycle ergometry test. You will be required to ride a cycle ergometer, maintaining a pedalling rate of 60 RPM. During the test, the resistance will be increased every two minutes until you can no longer maintain the pedalling rate. This test generally lasts ~8-12 minutes. For the duration of this test, you will be required to breathe into a mouthpiece (similar to a snorkel) for collection and analysis of expired breath. Heart rate will also be monitored via 3 chest electrodes.

Session 2 & 3 - Exercise at Specified Intensities

The second and third testing session will require you to report to the laboratory after a four hour fast. Resting blood pressure will then be taken and then a small Teflon catheter will be introduced into one of your arm arteries for the measurement of intra-arterial blood pressure. After a brief relaxation period, you will undergo 30 minutes of cycle ergometry at a power output which elicits either 50 or 75% (randomised order) of maximal oxygen consumption. To monitor this value, you will have to periodically breathe into the mouthpiece as above. Blood pressure will be measured by the intra-arterial catheter during exercise and for 2 hours post exercise. Additionally, blood samples (<2ml) will be drawn at rest, 15 and 30 minutes of exercise and 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post exercise for the determination of haematocrit. These blood samples will be drawn from the same catheter, which measures blood pressure and will pose no discomfort.

Session 4 - Muscle Sympathetic Nerve Activity

The final visit will require you to return to the laboratory and undergo an additional bout of ergometry at one of the previous cycling intensities. During this session, in addition to the blood pressure measurements as described above, microneurographic recordings of the peroneal and/or ulnar nerve will be performed prior to and following exercise. This will involve two small pieces of fine sterile wire to be inserted under your skin, one of which will be inserted into the nerve. This insertion may be accompanied by one of three brief, transient sensations a) a muscle twitch, b) a dull ache (similar to a tooth ache) or c) pins and needles. Each of these sensations will be alleviated with the movement of the electrode immediately upon indication.

Potential Risks:

Exercise may cause slight muscle strains and as with all exercise, there is a very slight risk of having a heart attack or collapsing. A supervised, adequate warm-up should alleviate the complication of muscle strains. The catheter insertion may cause slight bruising, but this will disappear within a few days. The catheter also imposes a risk of a blood clot to the hand. This could result in severe, permanent damage to the hand, including the loss of a finger. A published survey of complications from arterial catheterisation found a one in one thousand (1/1000) chance of a blood clot developing when the catheter was left in place for twenty-four hours. When this complication occurred, there was always complete resolution of the clot without residual damage. In this laboratory's experience, when the catheter has been in place for only a few hours, there has not been any complication related to a blood clot. A slight risk of infection related to the catheterisation of the artery also exists. This could result in a generalised infection of the body. However, this is only a very small potential risk. A recent survey did not find any evidence of infection, nor have any of the previous subjects in this laboratory suffered this complication. The risk associated with the micorneurographic electrode insertion into the peroneal nerve involves a slight chance (<10%) of a "pins and needles" feeling over the outside aspect of the foot. In Dr. Ettinger's hands, this has occurred in ~5% of participants and has always totally resolved within 2 days.

Withdrawal:

You are free to withdraw at any point during the study without repercussion. If you choose to withdraw, you will be permitted to view your collected data to date, after which point, that data will be destroyed.

Confidentiality:

The data will be stored inside a locked filing cabinet within a locked office located in the Human Performance Laboratory. Only the listed investigators will have access to this data.

Collected data will be used in the preparation of scientific manuscripts. You will in no way be identified in resulting publications or presentations

Remuneration:

You will be compensated $100.00 for your time commitment to this study.

Having read the above information, I consent to participate in all aspects of the study. I am aware that I am able to withdrawal at any time without repercussion.

Date	Signature
Date	Witness

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CONSENT FORM

Is post exercise hypotension preserved during periods of mild exercise simulating activities of daily living?

INVESTIGATORS	ADDRESSES	TELEPHONE
Dr. M.A. Tarnopolsky	Dept. of Kinesiology/Medicine	521-2100 x6367
Dr. J.D. MacDougall	Dept. of Kinesiology	x24647
Mr. J.R. MacDonald	Dept. of Kinesiology	x23016

Purpose:

We have recently found a drop in blood pressure after a single bout of exercise. This could lead to acute bouts of mild exercise being prescribed as a non pharmacological aid to hypertension. Unfortunately, to date, this drop in pressure has only been examined while subjects remained quietly seated after exercise. For this form of blood pressure control to have any clinical significance, it must occur while the patient is mobile and active as in daily living. In this study, we will compare the blood pressure responses after bouts of exercise and after seated rest during a post intervention period of mild exercise and simulated activities of daily living.

Procedure:

Session 1 - Maximal Oxygen Consumption

During the first testing session, you will undergo a cycle ergometry test. You will be required to ride a cycle ergometer, maintaining a pedalling rate of 60 RPM. During the test, the resistance will be increased every two minutes until you can no longer maintain the pedalling rate. This test generally lasts ~8-12 minutes. For the duration of this test, you will be required to breathe into a mouthpiece (similar to a snorkel) for collection and analysis of expired breath. Heart rate will also be monitored via 3 chest electrodes.

Session 2 & 3 - Exercise at Specified Intensities

The second and third testing session will require you to report to the laboratory after a four hour fast. Resting blood pressure will then be taken and then a small Teflon catheter will be introduced into your radial (wrist) artery for the measurement of intra-arterial blood pressure. After a brief relaxation period, you will undergo either a) 30 minutes of cycle ergometry at a power output which elicits 70% of maximal oxygen consumption (as found above). To monitor this value, you will have to periodically breathe into the mouthpiece as above or b) 30 minutes of seated rest (randomised order). Blood pressure will be measured by the intra-arterial catheter during exercise and for 1 hour post exercise. During the 1 hour post exercise period, you will be required to

perform bouts of very mild exercise and simulated activities of daily living (walking @ 3.5 mph, stair climbing (15 stairs), sitting and standing).

Potential Risks:
Exercise may cause slight muscle strains and as with all exercise, there is a very slight risk of having a heart attack or collapsing. A supervised, adequate warm-up should alleviate the complication of muscle strains. The catheter insertion may cause slight bruising, but this will disappear within a few days. The catheter also imposes a risk of a blood clot to the hand. A published survey of complications from arterial catheterisation found a one in one thousand (1/1000) chance of a blood clot developing when the catheter was left in place for twenty-four hours. When this complication occurred, there was always complete resolution of the clot without residual damage. In this laboratory's experience, when the catheter has been in place for only a few hours, there has not been any complication related to a blood clot. A slight risk of infection related to the catheterisation of the artery also exists. This could result in a generalised infection of the body. However, this is only a very small potential risk. A recent survey did not find any evidence of infection, nor have any of the previous subjects in this laboratory suffered this complication.
You will be monitored closely by a physician for 30 minutes after testing. Thereafter if you have any medical concerns, please call Dr. M. Tarnopolsky @ 521-2100 x 6443 or pager #2888.

Withdrawal:
You are free to withdraw at any point during the study without repercussion. If you choose to withdraw, you will be permitted to view your collected data to date, after which point, that data will be destroyed.

Confidentiality:
The data will be stored inside a locked filing cabinet within a locked office located in the Ivor Wynne Centre. Only the listed investigators will have access to this data.
Collected data will be used in the preparation of scientific manuscripts. You will in no way be identified in resulting publications or presentations

Remuneration:
You will be compensated $100.00 for your time commitment to this study.

Having read the above information, I consent to participate in all aspects of the study. I am aware that I am able to withdrawal at any time without repercussion.

_____	_____
Date	Signature
_____	_____
Date	Witness

McMaster University

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CONSENT FORM

Does serotonin contribute to post exercise hypotension?

INVESTIGATORS	ADDRESSES	TELEPHONE
Dr. J.D. MacDougall	Dept. of Kinesiology	x24647
Dr. M.A. Tarnopolsky	Dept. of Kinesiology/Medicine	521-2100 x6367
Jay R. MacDonald	Dept. of Kinesiology	x23016
Craig D. Hogben	Dept. of Kinesiology	523-5795

Purpose:

This study will examine possible causes for the drop in blood pressure that occurs after a single bout of exercise. This knowledge could lead to single bouts of mild exercise being used as a drug free aid to high blood pressure. To date, studies have been unable to find the cause of this drop in pressure.
Serotonin is a chemical in the brain that is known to be released during exercise. One of the effects of serotonin is to bind to specific receptors and cause a decrease in blood pressure. There is some evidence that the drop in blood pressure immediately after a single bout of exercise may be caused by serotonin. In this study, we will compare blood pressure responses after exercise under placebo ingestion and paroxetine HCl ingestion. Paroxetine HCl is a known inhibitor of serotonin re-uptake, therefore allowing more serotonin to be available in the brain and the circulation.

Procedure:

Session 1 - Maximal Oxygen Consumption
During the first testing session, you will undergo a cycle ergometry test. You will be required to ride a cycle ergometer, maintaining a pedalling rate of 60 RPM. During the test, the resistance will be increased every two minutes until you can no longer maintain the pedalling rate. This test generally lasts approximately 8-12 minutes. For the test, you will breathe into a mouthpiece (similar to a snorkel) for collection and analysis of expired breath. Heart rate will be monitored by 3 electrodes (tape patches) placed on the chest. You will also be asked to provide detailed diet records of all foods you consume over a four day period. This will allow us to provide you with pre-packaged diets for you for sessions 2 & 3.

Session 2 & 3 - Exercise at Specified Intensities
For seven to fourteen days prior to these sessions, you will take either paroxetine HCl or a placebo (randomised order) once daily. During the two days prior to each session, you will consume the provided pre-packaged diets. Please do not eat anything else. You will then report to the laboratory after a four hour fast. Resting blood pressure will be taken and then, after freezing the area with a small needle injection, a small Teflon catheter will be put into your radial (wrist) artery with a small needle (that will be removed) for the measurement of blood pressure. After a brief relaxation period, you will perform 30 minutes of cycling at 70% of maximum. To monitor this, you will have to occasionally breathe into the mouthpiece as above. Blood pressure will be measured through the catheter during

exercise and for 90 minutes post exercise. During the 90 minute post exercise period, you will remain quietly seated. Small samples of blood (approximately 7 ml) will be taken before exercise and at 5, 15, 30, 60 and 90 minutes post exercise.

Potential Risks:
Exercise may cause slight muscle strains and as with all exercise, there is a very slight risk of having a heart attack or collapsing. Stretching should decrease the chance of muscle strains. The catheter may cause slight bruising, but this will disappear within a few days. The catheter also imposes a risk of a blood clot to the hand. A published survey found a one in one thousand (1/1000) chance of a blood clot developing when the catheter was left in place for twenty-four hours. When this complication occurred, all clots were successfully dissolved without any damage to the hand. In this our laboratory, when the catheter has been in place for only a few hours, there has never been any complication related to a blood clot. A slight risk of infection related to the catheterisation of the artery also exists. This could result in a generalised infection of the body. However, this is only a very small potential risk. A recent survey did not find any evidence of infection, nor have any of the previous subjects in this laboratory suffered this. Paroxetine HCl is a prescription drug generally used to control depression. Although side effects are rare, those most commonly occurring are: nausea, sleepiness, sweating, tremor, dizziness, dry-mouth, constipation, diarrhoea, decreased appetite and ejaculatory delay (males). You are asked to notify the investigators immediately if you suffer from these side effects. This drug should **not** be taken if you are taking other serotonin effector drugs, MAO inhibitors or tryptophan. Do not take any of these substances within two weeks of taking paroxetine HCl, and consult your physician.
You will be monitored closely by a physician for 30 minutes after testing. Thereafter if you have any medical concerns, please call Dr. M. Tarnopolsky @ 521-2100 x 6443 or pager #2888.

Withdrawal:
You are free to withdraw at any point during the study without repercussion. If you choose to withdraw, you may view your collected data to date.

Confidentiality:
The data will be stored inside a locked filing cabinet within a locked office located in the Ivor Wynne Centre. Only the listed investigators will have access to this data.
Collected data will be used in the preparation of scientific manuscripts. You will in no way be identified in resulting publications or presentations

Remuneration:
You will be compensated $150.00 for your time commitment to this study.

Having read the above information, I consent to participate in all aspects of the study. I am aware that I am able to withdrawal at any time without repercussion.

Date	Signature
Date	Witness