THE RELATIONSHIP BETWEEN AEROBIC EXERCISE AND CARDIOVASCULAR STRESS REACTIVITY IN OFFSPRING OF HYPERTENSIVE FAMILIES

A thesis submitted in partial fulfilment of the requirements for the award of the degree DOCTOR OF PHILOSOPHY

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ABSTRACT

Individuals with a family history of hypertension are thought to be at greater risk from developing hypertension. A hyper-reactive response to stress has been demonstrated in offspring of hypertensive families that suggests heightened stress reactivity plays a role in the pathogenesis of hypertension. Although aerobic exercise is now commonly used as a non-pharmacological intervention for the treatment of essential hypertension, there is a paucity of research that has examined the relationship between exercise and risk markers of hypertension in offspring of hypertensive families. Thus, three studies were designed to examine this relationship.

Study I examined the cardiovascular response to orthostatic stress, mental stress, and a cold pressor test in highly (n =8) and moderately physically active (n = 10) males with a family history of hypertension. In Study II forearm blood flow reactivity and renal responses to mental stress were examined in highly (n =9) and moderately active (n = 9) males with a family history of hypertension. Study III examined the effects of acute exercise on stress reactivity in males with a family history of hypertension (n = 12). Impedance cardiography, an electrocardiogram, a Finapres blood pressure monitor, and plethysmography were used to examine cardiovascular variables.

In Study I the moderately active demonstrated significantly greater cardiopulmonary baroreceptor activity, forearm blood flow, and heart rate responses to mental stress compared to the highly active. In Study II the forearm blood flow response to mental stress was again significantly greater in the moderately active although there were no differences in renal responses. In Study III a post-exercise hypotensive response during recovery and stress was demonstrated. Also, the post-exercise forearm blood flow response to stress was significantly blunted.

The findings suggest that chronic and acute aerobic exercise is associated with lower forearm blood flow stress reactivity in males with a family history of hypertension. This may have implications for the risk of developing hypertension in genetically predisposed individuals.

Declaration

This thesis is the original work of the author, except where specifically referenced. No part of this thesis has been submitted previously, in any form, to this or any other Institution.

Mark Hamer

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION

Hypertension is generally defined as blood pressure persistently above 140/90 mmHg and is prevalent in 15-25% of the adult population in most countries (World Health Organisation, 1992). Cardiovascular risk and blood pressure are positively correlated with the higher the blood pressure the higher the risk of both stroke and coronary events (MacMahon, Petro, Cutler, & Collins 1990). Thus the control of hypertension is a major concern to world wide health organisations.

The lowering of blood pressure in hypertensive patients through the use of pharmacological treatment has been shown to significantly reduce the risk of stroke and myocardial infarction (Collins, Petro, MacMahon, & Cutler, 1990). However, there is evidence to suggest that some of these drugs have adverse effects which counteract the benefits of blood pressure reduction, such as increased LDL cholesterol (see Table 1.1). Therefore, non-pharmacological treatment of hypertension seems an attractive option. Whilst the majority of intervention studies have focused on reducing blood pressure in hypertensive patients, an increasing effort has been made to identify risk markers of hypertension that may be present in offspring of hypertensive parents. Thus, developing an effective non-pharmacological intervention to eliminate such markers before the disease develops may provide an attractive strategy in the early control of hypertension.

Table 1.1. Reductions in estimated 12-year risk of coronary heart disease resulting from different interventions in hypertensive patients. (Adapted from Hagberg & Brown, 1995).

	Characteristics after intervention				
	Initial Characteristics*	Diuretic	Diuretic plus β-blocker	β- blocker	Exercise training
Blood Pressure (mmHg)	160/100	140/90	140/90	140/90	150/90
Total Cholesterol ($mol.l^{-1}$)	6.2	6.6	6.6	6.2	5.9
HDL Cholesterol ($mol.l^{-1}$)	1.0	1.0	0.9	0.9	1.2
Estimated 12-year CHD risk** (%)	32	30	33	31	25.5

*Based on 55-yr old male smokers with no evidence of diabetes or left ventricular hypertrophy.

**Calculated from the equation of Anderson, Wilson, Odell, and Kannel (1991).

1.1 Rationale

1.1.1 The Role of Hyper-reactivity in Hypertension Development

The sympathetic nervous system (SNS) plays a pivotal role in rapid, short-term alterations in cardiovascular function during mental and physical stress. Specifically, during the 'defence' response a number of physiological changes are initiated in order to prepare the body for 'flight' or 'fight'. These include elevating cardiac output, through increasing heart rate, and skeletal muscle vasodilatation in order to provide the muscles with oxygen rich blood. Other changes involve activation of the renin-angiotensin system (RAS) in order to conserve sodium and thus promote conservation of water. Also, the defence response elicits insulin resistance in order to sustain adequate levels of blood sugar for the brain to function. These responses are thought to be driven by the SNS. However, although once vital to the survival of the organism, a hyper-responsivity of the defence reaction has been implicated in the development of hypertension, with the notion that repeated pressor episodes may elicit permanent hypertension (see Figure 1.1).

The elevated early risk of hypertension may be largely due to structural changes before the rise in blood pressure. Julius (1993) describes a 'hyperkinetic' circulation in the early developmental stages of hypertension that is characterised by an elevated heart rate, cardiac output, and plasma catecholamines. However, once the disease progresses into the hypertensive stage these central adaptations are no longer present, but instead an elevated peripheral resistance is observed. Vascular hypertrophy is thought to form the basis of this structural adaptation through genetic and structural reinforcement. Folkow (1987, 1990) proposed a process whereby minor overactivity of a pressor mechanism raises blood pressure and may initiate an abnormal hypertrophic response through genetic or trophic factors. Once the wall

thickness/ inner radius ratio of the vessel is increased this gives rise to an amplifier effect when the vessel is subjected to vasoconstrictor stimuli. Thus, luminal narrowing is accentuated in proportion to the wall/inner radius increase. Three elements of this hypothesis are supported by clear evidence: the existence of vascular hypertrophy in hypertension; the ability of increased pressure to cause hypertrophy; and the ability of hypertrophy to amplify a pressor signal in preparations of isolated perfused vessels.

A further factor in the development of hypertension through a hyper-reactive mechanism is the role of the kidney. High levels of renal sympathetic nervous activity (SNA) can shift the pressure natriuresis curve and facilitate the maintenance of hypertension by interfering with the ability of the kidney to compensate for an increase in arterial pressure through pressure natriuresis.

There is no direct evidence to support a causative role for hyper-reactivity in the development of hypertension but there is indirect evidence that hyper-reactivity may play some role, for example in combination with another pathological factor or may impact only in those individuals who are genetically predisposed. The suggestion that hyper-reactivity might play a greater role in the development of hypertension in individuals that are genetically vulnerable is supported by findings of increased reactivity in offspring hypertensives (Turner, 1994). Miall (1971) suggested that family history of hypertension is a key risk factor, identifying familial factors as accounting for a third of the variance of systolic pressure and a fifth of that of diastolic. Longitudinal studies have further underlined the importance of family history as a risk factor of hypertension. For example, Falkner, Kushner, Onesti, and Angelakos (1981) followed up 50 adolescents who met the initial criteria of borderline hypertension (blood pressures in the range of 90^{th} to 95^{th} percentile).

Within 4 years 56% progressed to a state of sustained hypertension (blood pressures repeatedly above the 95th percentile for more than 3 months), of which all had a positive family history of hypertension. Thus, hyper-reactivity to mental stress in individuals with a family history of hypertension may be a key risk marker in the early development of hypertension.

1.1.2 Role of Exercise in Reducing Risk Markers of Hypertension

One of the largest epidemiological studies carried out in the United States (Paffenbarger, Wing , Hyde, & Jung, 1983) provided compelling evidence that normotensive individuals with a low level of physical activity or fitness have an increased risk of developing hypertension. Further, longitudinal evidence suggests that former endurance trained athletes have significantly lower resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) than their more sedentary counterparts (Pyörälä *et al.*, 1967). A large number of intervention studies have been performed on the effects of exercise on blood pressure. The overall consensus in the literature published to date is that endurance exercise reduces both SBP and DBP in 75% of hypertensive patients. These reductions average approximately 10 mmHg for both SBP and DBP (see Table 1.2). Meta-analyses that only include studies employing randomised trials (Halbert, Silagy, & Finucane, 1997; Kelly & McClellan, 1994) have shown reductions in SBP of 7-4 mmHg and DBP of 6-4 mmHg. It has been shown that a reduction in DBP of 5-6 mmHg by pharmacological treatment is associated with a 42% reduction in the incidence of stroke and a 14% reduction in coronary heart disease (Collins *et al.*, 1990). Thus, taking into account unknown individual and environmental factors, exercise training seems to be an affective strategy to both reduce the risks associated with hypertension and reduce the potential risk to develop hypertension. However, the mechanisms associated with the anti-

hypertensive and potential protective effects of exercise training are not clearly understood.

Table 1.2. Dose-response relationships between exercise and blood pressure according to the intensity and duration of exercise-training programme. (Adapted from Hagberg & Brown, 1995).

	Training intensity ($\dot{V}O_{2max}$)		Exercise training duration (weeks)		
	< 70%	>70%	1-10	11-20	21+
Systolic blood pressure					
Average reduction (mmHg)†	9.5	6.8	9.5	11.1	10.9
Groups with significant reductions (%)	64	75	71	65	64
Total sample size	383	286	336	440	145
Diastolic blood pressure					
Average reduction (mmHg)‡	7.0	6.8	7.1	9.3	9.6
Groups with significant reductions (%)	78	73	79	74	75
Total sample size	477	237	357	418	159

† Average across studies whose participants initially had SBP in excess of 140 mmHg.

‡ Average across studies whose participants initially had DBP in excess of 90 mmHg.

The average was computed by weighting for the sample size of each study. Studies with a non-significant reduction in blood pressure were entered as zero change, and their sample size was added into the final sample size.

Current anti-hypertensive mechanisms of exercise have focused on adaptations to the SNS (see Chapter 2 for more detail). If exercise is to play a role in reducing the risk of hypertension in offspring hypertensives then this may involve an exercise induced mechanism that results in a reduction in SNS hyper-reactivity. Therefore, three studies were designed to investigate the effects of physical activity and acute exercise on hypertension risk markers in offspring hypertensives. Previous research has identified the detrimental effects of a hyper-reactive SNS on the cardiovascular system as a potential risk for the development of hypertension (see Chapter 2). Thus, Study I assessed cardiovascular functioning in moderately and highly active offspring hypertensives during a number of physical and mental stressors designed to activate different aspects of the SNS. It was predicted that the moderately active offspring hypertensives would demonstrate hyper-reactive responses to the various challenges in comparison with the highly active offspring hypertensives. In Study II cardiovascular and renal responses to mental challenge were investigated. It was predicted that the moderately active offspring hypertensives would be more reactive to the mental challenge and also display sodium retention due to a higher activation of the RAS. Study III examined the effect of acute exercise on the cardiovascular response to mental challenge in moderately active offspring hypertensives. It was predicted that acute exercise would significantly lower cardiovascular reactivity to mental challenge. Throughout the studies a common theme was to focus on the effects of acute exercise/physical activity and not components of fitness such as maximal oxygen uptake as this has a high genetic component. It was postulated that using physical activity measures as opposed to fitness scores to determine the different groups in the cross-sectional designs would infer that the effects of acute exercise

may be a more important determinant of the stress response than genetic fitness or chronic training adaptations.

1.2 Aims

The specific aims of these studies are to:

I.a) Compare cardiopulmonary baroreceptor function in moderately and highly active offspring hypertensives.

I.b) Compare cardiovascular reactivity to mental challenge and cold pressor test in moderately and highly active offspring hypertensives.

II.a) Compare cardiovascular reactivity to an extended mental challenge in moderately and highly active offspring hypertensives.

II.b) Compare renal responses to mental challenge in moderately and highly active offspring hypertensives.

III.a) Examine the effects of acute exercise on cardiovascular reactivity to mental challenge in moderately active offspring hypertensives.

1.3 Hypotheses

It is hypothesised that:

I.a) Moderately active offspring hypertensives will display significantly augmented cardiopulmonary baroreceptor function in comparison with highly active offspring hypertensives.

I.b) Moderately active offspring hypertensives will display significantly higher levels of cardiovascular reactivity to mental challenge and cold pressor test in comparison with highly active offspring hypertensives.

II.a) Moderately active offspring hypertensives will display significantly higher levels of sustained cardiovascular reactivity to an extended mental challenge in comparison with highly active offspring hypertensives.

II.b) Moderately active offspring hypertensives will display sodium retention in response to mental challenge in comparison with highly active offspring hypertensives who will display sodium excretion.

III.a) Acute exercise will significantly lower the cardiovascular reactivity response to mental challenge in moderately active offspring hypertensives.

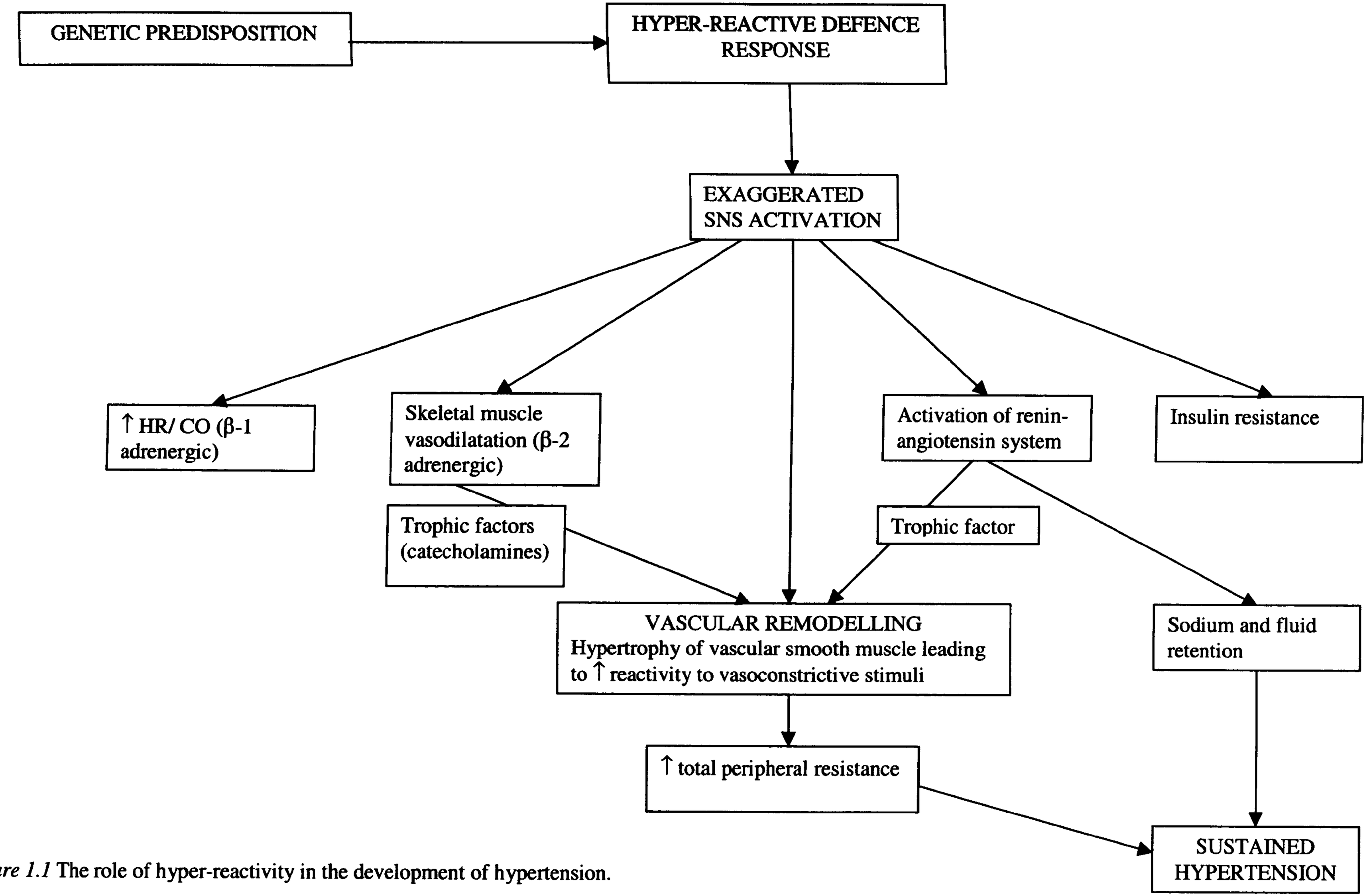


Figure 1.1 The role of hyper-reactivity in the development of hypertension.

CHAPTER 2

REVIEW OF LITERATURE

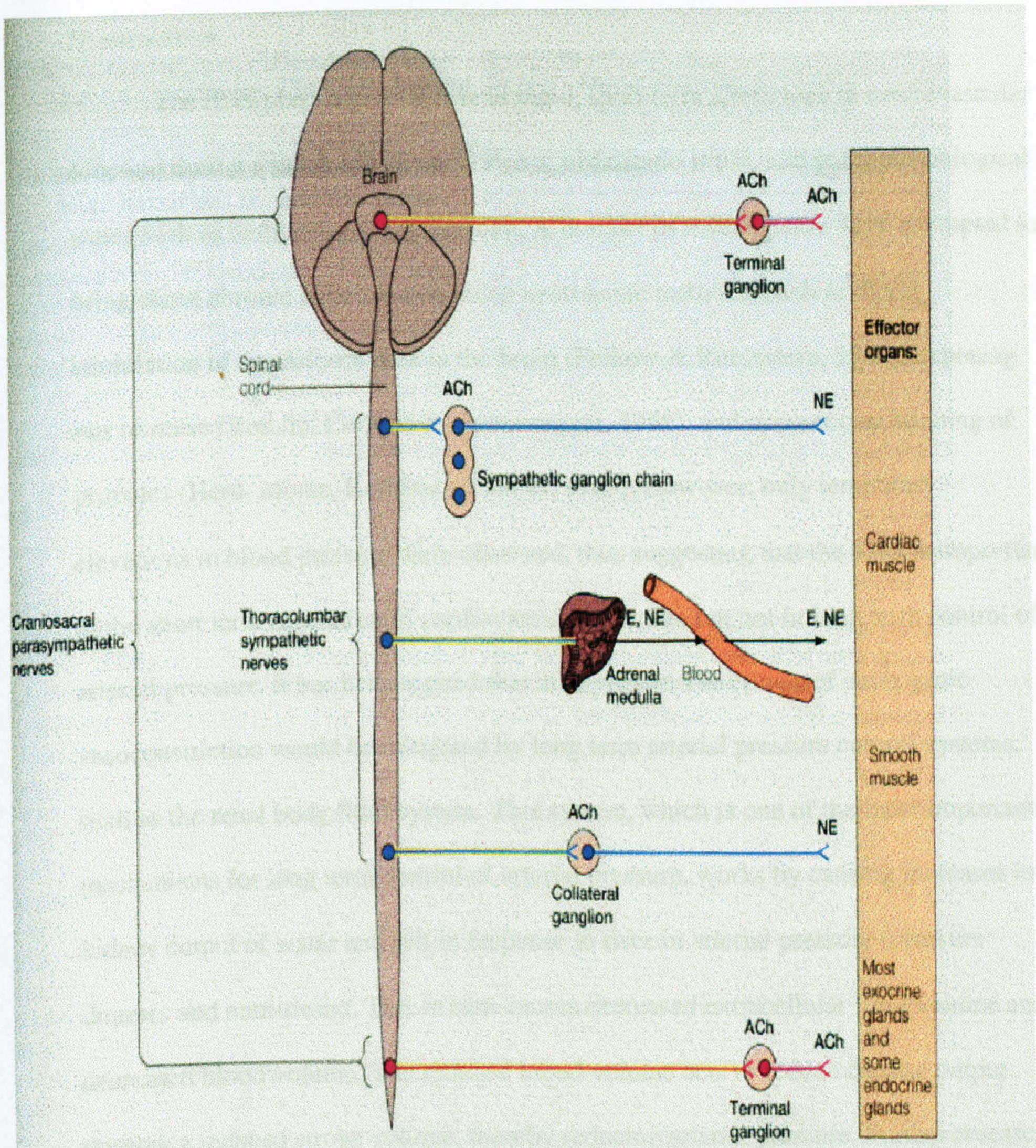
In order to elucidate potential risk markers of hypertension in offspring hypertensives it is important to consider possible factors involved in the pathophysiology of essential hypertension. Therefore, the first part of the review will focus on the role of sympathetic nervous activity (SNA) in the early development of hypertension covering the importance of SNA in the pathogenesis of hypertension, evidence for heightened SNA in offspring hypertensives, and potential mechanisms for increased SNA. The second part of the review will consider the potential interaction between genetic predisposition for hypertension and the environment covering the role of diet, stress, and exercise in hypertension risk. Finally, the third section will review the anti-hypertensive and stress reactivity reducing mechanisms of exercise in order to identify a potential exercise related mechanism for eliminating hypertension development.

2.1 The Sympathetic Nervous System and Hypertension Development

2.1.1. Anatomy and Neurotransmitters

The sympathetic nervous system (SNS) together with the parasympathetic nervous system forms the autonomic nervous system (ANS). Sympathetic nerve fibres originate in the thoracic and lumbar regions of the spinal cord (see Figure 2.1). Each sympathetic pathway extending from the central nervous system to an innervated organ consists of a two-neurone chain. Preganglionic fibres release acetylcholine and postganglionic fibres release norepinephrine. Most preganglionic axons of the sympathetic branch synapse with postganglionic axons within the sympathetic ganglion chain, however, some run to collateral ganglion located near to the effector

organ. Another important sympathetic neurotransmitter is epinephrine that is released into the blood by the adrenal gland. The adrenal gland is considered to be a modified sympathetic ganglion that does not give rise to post ganglionic fibres. Instead, it secretes hormones into the blood (80% epinephrine, 20% norepinephrine) upon stimulation by preganglionic fibres that originate in the central nervous system. Epinephrine and norepinephrine bind to specific adrenergic receptor sites at the effector organ. α and β-1 adrenergic receptors bind with both epinephrine and norepinephrine, whereas β-2 receptors bind primarily with epinephrine.



ACh = Acetylcholine NE = Norepinephrine E = Epinephrine

Figure 2.1. The anatomy and neurotransmitters of the autonomic nervous system

2.1.2. Importance of the Sympathetic Nervous System in the Pathogenesis of Hypertension

The SNS plays a pivotal role in rapid, short term alterations in cardiovascular function during mental and physical stress, orthostatic stress, and pathophysiological states such as hemorrhagic hypotension. A number of investigators have attempted to bring about chronic hypertension using neurogenic methods, such as direct stimulation of the defence area in the brain (Folkow & Rubinstein, 1966), exposing rats to noise (Rothlin, Cerletti, & Emmenegger, 1956), and operant conditioning of primates (Herd, Morse, Kelleher, & Jones, 1969). However, only temporary elevations in blood pressure were observed, thus suggesting that the SNS is important in the short term regulation of cardiovascular function but not in long term control of arterial pressure. It has been argued that the hypertensive effects of neurogenic vasoconstriction would be mitigated by long term arterial pressure control systems, such as the renal body fluid system. This system, which is one of the most important mechanisms for long term control of arterial pressure, works by causing increases in kidney output of water and salt in response to rises in arterial pressure (pressure diuresis and natriuresis). This in turn causes decreased extracellular fluid volume and decreased blood volume. The reduced blood volume acts to reduce cardiac output through a reduced stroke volume, thereby reducing arterial pressure. Further research has implicated the role of hyper-reactivity in the development of hypertension, with the notion that repeated pressor episodes may bring about permanent hypertension. There is no direct evidence to support a causative role for hyper-reactivity in the development of hypertension, but there is indirect evidence that hyper-reactivity may play some role, for example in combination with another pathological factor, or may impact only in those individuals who are genetically predisposed. The suggestion that

hyper-reactivity might only play a significant role in the development of hypertension in individuals that are genetically vulnerable is supported by findings of increased reactivity in offspring hypertensives (Turner, 1994).

There are a number of other neuroeffector mechanisms that may influence the long term regulation of blood pressure. The renal sympathetic nerves not only cause renal vasoconstriction but also enhance the release of renin and promote reabsorption of sodium and water from the renal tubules. Thus, high levels of renal SNA can shift the pressure natriuresis curve and facilitate the maintenance of hypertension by interfering with the ability of the kidney to compensate for an increase in arterial pressure through pressure natriuresis. The SNS can also exert long term trophic effects on vascular muscle (Bevan, 1984; Lever, 1986), thus causing structural changes in blood vessels that increase vascular resistance and the vasomotor response to vasoconstrictor stimuli.

2.1.3 Evidence of Heightened Sympathetic Nervous Activity in Offspring Hypertensives

The detrimental effects of psychological stress are generally ascribed to SNA and its concurrent effects on cardiac rhythmicity (Verrier, 1987), the vascular endothelium (Clarkson, Kaplan, Adams, & Manuck, 1987), arterial blood pressure (Folkow, 1978), and lipid mobilisation (Eliot, 1987). There is an increasing body of evidence to support heightened SNA in offspring hypertensives during mental and physical stressors (see review by Muldoon, Terrell, Bunker, & Manuck , 1993). However, the majority of research in this area is equivocal.

2.1.3.1 Heart rate and blood pressure reactivity. Out of the 51 family history studies in hypertension that specifically looked at heart rate and blood pressure reactivity to mental stress (reviewed by Muldoon *et al.*, 1993) only a third of the

studies documented greater reactivity in white males with positive family history compared to those with negative family history. Additionally, among black males, blood pressure reactivity to a psychological stressor has failed to differentiate individuals with and without family history of hypertension in nearly all comparisons reported. Similarly, when examined in relation to family history of hypertension, the cold pressor test yields equivocal results, with only 6 of 15 reviewed investigations reporting greater blood pressure or heart rate responses in subjects with a positive history. Moreover, reactivity to physical stressors has produced a similar pattern of findings; heart rate and blood pressure responses to sustained handgrip (isometric exercise) at loads ranging from 20 to 60% of maximum voluntary contraction and over intervals of 90 s to 5 min have produced positive findings in four of nine reviewed studies. Of these positive findings the results have shown a larger systolic blood pressure rise (Manuck & Proietti, 1982), a larger diastolic blood pressure rise (McCann & Matthews, 1988; Stoney & Matthews, 1988), and a larger heart rate response (Allen, Lawler, & Mitchell, 1987) in offspring hypertensives. Responses to dynamic exercise, including treadmill, supine and upright bicycle ergometry exercise have produced positive findings in four of eight reviewed studies. The positive findings suggest an increased systolic blood pressure response during submaximal or maximal exercise in offspring hypertensives (Alli, Avanzini, & DiTullio, 1990; Molineux & Steptoe, 1988; Nielson, Gram, & Pederson, 1989; Saito, Koshibu, & Kai, 1989). These inconsistencies may be due to weak study design, such as failure to confirm and report blood pressures of family members. Also, the stronger studies have employed the more powerful comparison of strong versus absent family history (biparental hypertension versus biparental normotension).

2.1.3.2 Cardiovascular patterning. A further point to consider when analysing the studies documenting reactivity to a psychological stressor is the different type of stressors that are employed, and the specific cardiovascular patterns that they elicit. All the stressors employed are designed to increase blood pressure, but the majority of studies do not consider the different combinations of changes in cardiac output and vascular resistance which give rise to the increased blood pressure. For example, a memory search reaction time task is intended to evoke a predominantly β-adrenergic cardiac response, whereas a visual search reaction time task is intended to evoke both β-adrenergic and α-adrenergic vascular responses. De Visser *et al.* (1995) employed these two types of mental stressor to study cardiovascular responses in 56 offspring hypertensives (all with two hypertensive parents) and 43 control subjects (all with two normotensive parents). All subjects were healthy with normal blood pressure (mean age 22± 0.7 years). They found no evidence to support the presence of hyperadrenergic activation of the heart in offspring hypertensives during the memory task. However, during the visual search task, offspring hypertensives were characterised by enhanced peripheral vascular resistance. Stoney and Matthews (1988) observed an exaggerated diastolic blood pressure response in middle aged male and female offspring hypertensives during a variety of stressors, which included a memory task, visual search task, and isometric hand grip. The authors concluded that the greater diastolic blood pressure response was related to an exaggerated α-adrenergic peripheral resistance response.

2.1.3.3 Vascular reactivity. Other researchers have employed the plethysmographic method to measure limb blood flow during mental challenge. Ohlsson (1982) observed a decreased hand blood flow in offspring hypertensive subjects, using a tone reaction task. Also, a number of researchers (Anderson,

Mahoney, Lauer, & Clarke, 1987; Miller & Ditto, 1991) have observed an exaggerated forearm blood flow response during mental challenge in offspring hypertensives. The results from Miller and Ditto (1991) strongly implicated the sympathetic nervous system in the exaggerated cardiovascular response to stress in offspring hypertensives. Their study employed the use of selective pharmacological blockade, a β-1 adrenergic blocker and an α-1 adrenergic blocker. The study compared heart rate and forearm blood flow response between offspring hypertensives and controls during a 1-hr active coping psychological stressor under a placebo and two drug conditions. Under the placebo condition the offspring hypertensives demonstrated exaggerated heart rate and forearm blood flow responses to the stressor. Under the β-1 adrenergic blocking condition only differences in heart rate response were abolished. Under the α-1 adrenergic blocker the responses were similar to that observed under the placebo condition for the first 15 min although during the last 15 min, the α-1 blocker eliminated the rise in forearm vascular resistance observed in offspring hypertensives under the placebo condition. These results suggest that the initial forearm vasodilatory response to stress and the reductions in forearm vascular resistance are reinforced by β-2 adrenergic or cholinergic activity and that later increases in forearm vascular resistance may reflect increasing α-1 adrenergic activity. Further studies indicate exaggerated vascular or pressor responses, or lower threshold response to infused norepinephrine in offspring hypertensives (Bianchetti, Weidmann, Beretta-Piccoli, 1984; De Lima, Dias, Bernardes-Silva, & Belloti, 1990; Doyle & Fracerm, 1961). Thus, overall results confirm that offspring hypertensives exhibit α-1 and β-adrenergic hypersensitivity.

2.1.3.4 Renal haemodynamics. Differences in renal functioning between offspring hypertensives and controls both at rest (van Hooft *et al.*, 1991) and during

mild mental challenge (Hollenburg, Williams, & Adams, 1981) have been observed. Van Hooft *et al.* (1991) observed lower renal blood flow and suppressed renin and aldosterone concentrations in offspring hypertensives at rest. Hollenburg *et al.* (1981) observed reduced renal blood flow and increases in renin, aldosterone, and angiotensin during mental stress in offspring hypertensives, which were even more pronounced in hypertensive subjects. Altered renal functioning has been closely related to vascular reactivity and the potential development of hypertension.

Activation of the renal α-adrenergic receptors is thought to induce sodium retention through activation of the renin-angiotensin-aldosterone system causing renal constriction (DiBona, 1982, 1985). An altered sodium balance may result in enhanced vascular responsiveness to sympathetic nervous activation due to disturbed endothelial mechanisms (Blaustein & Hamlyn, 1984; Haddy, 1974). The exaggerated sodium re-absorption results in a tendency towards sodium, water, and extracellular fluid volume expansion that is compensated for by the secretion of a natriuretic hormone. This hormone promotes sodium excretion by inhibiting sodium pumps in the kidney tubules and is also responsible for the inhibition of the sodium pump in vascular smooth muscle cells. Increases in intracellular sodium are then followed by increases in intracellular free calcium concentrations, resulting in elevated vascular tone and an exaggerated vascular responsiveness to endogenous vasoconstrictive agents. Such a response over time may result in vascular hypertrophy that would cause increases in vascular resistance. These resistance type changes are identifiable in established hypertension, whilst in contrast, an increased cardiac output is more characteristic in the early phases of hypertension development (Julius, 1991).

2.1.4 Potential Mechanisms for Heightened Sympathetic Nervous Activity in Offspring Hypertensives

There are a number of mechanisms that may explain the findings of heightened SNA which include an increased release of the sympathetic neurotransmitters, and/or increased tissue sensitivity. Resting plasma catecholamine concentrations are not consistently elevated in offspring hypertensives compared with controls (see Muldoon *et al.*, 1993). However, it remains questionable whether catecholamine plasma levels are a good indicator of SNA. Using microneurographic recordings, which is perhaps more representative of SNA, Yamada *et al.*, (1988) showed that resting muscle sympathetic nerve activity (MSNA) was higher in offspring hypertensives than in controls.

A widely held belief is that elevated levels of SNA may result from impaired baroreceptor restraint on sympathetic neural outflow. Matsukawa *et al.*, (1988) found that the slopes of the relations between arterial pressure and muscle SNA after phenylephrine injections are lower in hypertensives than in normotensive subjects. Also, in borderline hypertensives, increased levels of MSNA are related inversely to vagal baroreflex slopes. However, abnormalities in baroreceptor control of parasympathetic activity (heart rate) do not necessarily indicate abnormalities in baroreceptor control of SNA and vascular resistance, as shown by Guo, Thames, and Abboud (1983). Parmer, Cervenka, and Stone (1992) measured baroreflex control of the heart rate in offspring hypertensives and controls and found that baroreflex sensitivity was lower in offspring hypertensives. Offspring hypertensives have also been found to display abnormalities in cardiopulmonary (C-P) baroreceptor function, shown by an exaggerated forearm vasoconstrictor response when the C-P baroreceptors are unloaded during mild levels of lower body negative pressure (Ueda

et al., 1989). Thus, it has been suggested that the C-P baroreceptors may act to buffer a heightened sympathetic neural drive caused by arterial baroreceptor dysfunction (Mark & Kerber, 1982).

A second important mechanism is sensitivity to adrenergic stimulation. Using radioligand binding techniques, Michel, Galal, Stoermer, Block, and Brodde (1989) showed that platelet α-2 adrenoceptor density was significantly increased in children with family history of hypertension (9.19 ± 0.73 years) compared with controls. This provides strong evidence to support a model for the pathogenesis of genetically determined hypertension.

2.2 Interaction of Genetic Predisposition and the Environment

There is substantial evidence to suggest that exaggerated reactivity to psychological stress in combination with an interaction of genetic and environmental factors may be a potential risk marker of hypertension. The following section will review the interaction of family history of hypertension, diet, exercise, and stress.

2.2.1 Hypertension Risk and Diet

Miller, Friese, and Sita (1995) studied the effect of sodium loading and parental history of hypertension on the cardiovascular response to stress. In offspring hypertensives sodium loading elevated total peripheral resistance and norepinephrine response to stress relative to placebo conditions and compared with controls. However, the relationship between dietary salt intake and the development of hypertension has been the subject of continuing debate. Despite abundant epidemiological, experimental, and interventional observations demonstrating a link between salt and hypertension, scepticism remains. This is based on the observation that not all individuals have demonstrable changes in blood pressure after ingestion of increased or decreased amounts of sodium chloride (Weinburger, 1996). Brum,

Tramposch, and Ferrario (1991) have also suggested that sodium may play no direct role in the pathogenesis of hypertension but may be a marker of an underlying activation of central neural and endocrine mechanisms.

2.2.2 Hypertension Risk and Exercise

A number of studies have examined whether a high level of cardiovascular fitness/ chronic exercise training and acute exercise may prevent daily stress from exerting its negative influence on cardiovascular health by reducing SNA.

2.2.2.1 Chronic exercise effects on stress reactivity. Research to date, using both cross-sectional and longitudinal designs, in normal populations is equivocal. A review of the cross-sectional research comparing reactivity of trained and untrained subjects suggests that about half of the studies show a reduced heart rate reactivity to a variety of laboratory stressors in the trained (Holmes & McGilley, 1987; Holmes & Roth, 1985; Light, Obrist, James, & Strogatz, 1987; Turner, Costello, Carroll, & Sims, 1987; van Doornen & de Geus, 1989), whereas others found no differences (Brooke & Long, 1987; Cox, Evans, & Jamieson, 1979; Dorheim, Ruddel, & Elliot, 1984; Hollander & Seraganian, 1984; Hull, Young, & Ziegler, 1984; Plante & Karpowitz, 1987; Sinyor, Peronnet, Brisson, & Seraganian, 1986; Sothmann, Horn, Hart, & Gustafson, 1987). However, an ongoing issue in the literature is whether heart rate responsivity or absolute heart rate level during stress is more important. All of the aforementioned studies report a lower absolute heart rate level during stress in the high fit subjects. This finding has been hugely overlooked and may be a key factor. Lower heart rates in the trained are thought to be due to an enhanced cardiac parasympathetic influence and the relative balance of autonomic control between parasympathetic and sympathetic may be important during stress. Boutcher, Nugent, McClaren and Weltman (1998) reported that trained males exhibited a greater phasic

decrease in respiratory sinus arrhythmia (RSA), compared to untrained, during the Stroop mental challenge. This suggests that trained individuals possibly have a lower activation of the SNS during stress, and show a greater reliance on the parasympathetic system.

Longitudinal designs in this area have provided no clear evidence to suggest exercise training reduces stress reactivity. However, there are a number of issues to be considered in the comparison of cross-sectional and longitudinal design. First, the selection of highly fit versus low fit individuals may confound the psychological effects of aerobic fitness on autonomic functioning per se with the psychological effects of sport and exercise participation on the appraisal of the stressor. Secondly, aerobic fitness has a large genetic component, and therefore the causal role of exercise training per se, on stress reactivity, using a cross-sectional design is questionable. It may be that stress reactivity also has a strong genetic component. These issues were raised by de Geus, van Doornen, De Visser, and Orlebeke (1990), when they studied the effect of existing and training induced differences in aerobic fitness on reactivity to stress. The authors firstly used a correlational design to study the relationship between aerobic fitness ($\dot{V}O_{2max}$) and cardiovascular reactivity to a series of stressors. They found that the decrease in RSA during tasks was smaller in more fit subjects ($r = 0.4$, $P < 0.05$), suggesting that vagal inhibitory influences on the heart remained more intact. However, changes in heart rate, cardiac output, stroke volume, total peripheral resistance, and blood pressure during tasks were not significantly related to fitness level. Subjects were then randomly assigned to a running and indoor fitness training programme (1.5 hr, 4 day.week^{-1}, 7 weeks), or a wait-listed control group. The results showed no effect of endurance training on the reactivity of any variables. That pre-existing levels of aerobic fitness, in a sample of sedentary subjects, was

more highly related to reactivity levels, compared with the effects of regular exercise training suggests that stress reactivity is pre-disposed. However, the findings may be explained in light of the relatively low training induced increases in $\dot{V}O_{2max}$ of 5 $ml.kg^{-1}.min^{-1}$, compared with the larger range of 30 $ml.kg^{-1}.min^{-1}$ in the correlational analysis. Subjects in the training group also seemed to start with a moderate level of fitness ($\dot{V}O_{2max}$: 46.6 ± 5.6 $ml.kg^{-1}.min^{-1}$, heart rate: 62.8 ± 6.4 $b.min^{-1}$), which may suggest that training will only induce reactivity changes in low fit subjects, or possibly only in those who are highly reactive, such as hypertensive patients and offspring hypertensives. Indeed, subjects in the aforementioned studies have all been healthy, young, normotensive individuals. In one of the few studies that has examined the effect of chronic exercise on stress reactivity in hypertensive subjects, systolic and diastolic blood pressure, total peripheral resistance, and heart rate were significantly reduced during mental stress after six months of aerobic exercise training in comparison with the control subjects (Georgiades *et al.*, 2000).

2.2.2.2 Acute exercise effects on stress reactivity. The rationale behind studying the effects of acute exercise on stress reactivity is that acute effects may accumulate over a training programme to generate sustained differences. The acute reduction of blood pressure that follows vigorous exercise is well documented (for review see Kenney & Seals, 1993). Repeated exposure to hypotensive episodes through exercise training are hypothesised to reduce total hemodynamic load producing cardiovascular benefits. However, in the case of stress reactivity, the research to date is again equivocal. There seems to be more evidence though to support an acute exercise stress reactivity lowering effect than that of chronic exercise. This is possibly due to the absence of the confounding variable genetic fitness that has been problematic in the case of chronic exercise studies. Out of the 10

studies reviewed, eight showed a stress reactivity lowering effect to mental challenge after an acute bout of exercise (Boone, Probst, Rogers, & Berger, 1993; Ebbesen, Prkachin, Mills, & Green, 1992; Probst, Bulbulian, & Knapp, 1997; Roy & Steptoe, 1991; Rejeski, Gregg, Thompson, & Berry, 1991; Rejeski, Thompson, Brubaker, & Miller, 1992; Steptoe, Kearsley, & Walters, 1993; West, Brownley, & Light, 1998), whereas the remainder of studies showed no effect (Perronet, Massicotte, Paquet, Brisson, & de Champlain, 1989; Roth, 1989). The stress reactivity lowering effects of acute exercise have mainly been observed as a reduction in blood pressure reactivity, although West *et al.* (1998) also noted a post exercise reduction in total peripheral resistance which persisted during the stress period. Also, Probst *et al.* (1997) noted a reduction in heart rate reactivity to stress in the post exercise condition. However, this may have been due to the higher initial pre-stress heart rate level from the exercise, which may have blunted the response. The lack of significant findings in some studies may be related to the intensity and duration of exercise employed and the variation in timing of the post exercise reactivity test. It seems those studies reporting significant findings have generally employed higher intensity exercise (>60% $\dot{V}O_{2max}$) for at least 20 minutes and completed reactivity testing within the first hour of exercise recovery. For example, Steptoe *et al.* (1993) employed two different exercise intensities (50 and 70% $\dot{V}O_{2max}$) but only found a significant stress reactivity lowering effect for the higher intensity.

2.2.2.3 Exercise effects in offspring hypertensives. There is a paucity of research that has specifically looked at the effects of fitness and exercise training on stress reactivity in individuals with a familial history of hypertension. Holmes and Cappo (1987) provided evidence to suggest that aerobic fitness may play a role in preventing high levels of stress reactivity in offspring hypertensives. The research

employed a cross-sectional design with a cohort of 70 normotensive collegiate males, which were split into three categories; the ten most fit offspring hypertensives ($\dot{V}O_{2max}$: 50.13 ml.kg^{-1}.min^{-1}), the 10 least fit offspring hypertensives ($\dot{V}O_{2max}$: 26.88 ml.kg^{-1}.min^{-1}), and 21 controls with normotensive parents ($\dot{V}O_{2max}$: 38.98 ml.kg^{-1}. min^{-1}). Heart rate and blood pressure reactivity were measured during a series of mental challenges, which included recall of digits backwards, a vocabulary test, mental arithmetic, Stroop colour/word naming, and a mathematical information task. The authors found that during the stress period, offspring hypertensives who were classified as high fit demonstrated similar levels of reactivity compared with the controls, and both of these groups demonstrated lower levels of reactivity compared with the offspring hypertensive low fit group. However, the offspring hypertensive low fit group had a significantly lower fitness level compared with the controls ($\dot{V}O_{2max}$: 26.88 versus 38.98 ml.kg^{-1}.min^{-1} respectively) that may have confounded the findings. Thus, whether the higher level of cardiovascular stress reactivity observed in the offspring hypertensive low fit group was attributable to low fitness *per se* or the effect of family history cannot be reliably ascertained. Nevertheless, the findings are supportive of a role for moderate levels of fitness in the protection against risk markers of hypertension. It is important to note that although the "most fit" individuals were classified as a "high fit" group, the mean maximal oxygen uptake score was only 50.13 ml.kg^{-1}.min^{-1} which represents a highly active but not highly trained level of aerobic fitness. The dose response relationship between exercise and reduction of hypertension risk may be an important issue considering the problems of adherence to an exercise programme.

Two other studies have attempted to examine the moderating effects of aerobic fitness on the autonomic nervous system in offspring hypertensives

(Buckworth, Convertino, Cureton, & Dishman, 1997; Buckworth, Dishman, & Cureton, 1994). Buckworth *et al.* (1994) recruited 31 offspring hypertensive females (18 to 30 years old) and classified them by fitness and also activity level. Fitness was estimated from a graded maximal treadmill test, and subjects were assigned to either the highly fit group ($\dot{V}O_{2max}$: 46.62 ± 6.5 $ml.kg^{-1}.min^{-1}$, range 39.1 to 60.9 $ml.kg^{-1}.min^{-1}$), or the moderately fit group ($\dot{V}O_{2max}$: 35.89 ± 1.9 $ml.kg^{-1}.min^{-1}$, range 33.3 to 38.9 $ml.kg^{-1}.min^{-1}$). Subjects were also separately assigned into a highly active (1217 ± 98.4 $J.kg^{-1}.week^{-1}$) or moderately active (1015.5 ± 49.4 $J.kg^{-1}.week^{-1}$) group, estimated from the recall of the previous weeks physical activity. Heart rate and blood pressure were measured during mental arithmetic and cold face testing, and on a separate occasion the same tests were performed whilst the carotid-cardiac baroreflex was stimulated. In contrast to Holmes and Cappo (1987), no differences were observed in heart rate or blood pressure reactivity responses to mental arithmetic or the cold-face test between groups representing different levels of fitness and physical activity. This discrepancy is possibly due to the smaller separation in fitness levels in the Buckworth *et al.* study. However, despite the lack of difference in reactivity, the highly fit women had longer R-R intervals compared with the moderately fit women during stimulation of the carotid-cardiac baroreflex at rest. Also, the carotid-cardiac baroreflex was attenuated during mental arithmetic compared with rest in both the moderately active and moderately fit women but not in the highly active and highly fit groups. Thus, the latter findings suggest that physical activity and cardiorespiratory fitness may help regulate blood pressure during stress by enhancing parasympathetic tone. More specifically, these findings provide evidence to suggest physical activity or exercise training may prevent the abnormalities in baroreflex control that have been observed among offspring hypertensives.

In a follow up study by Buckworth *et al.* (1997), again using offspring hypertensive females, an experimental design was employed to further substantiate a causal role of exercise training in reducing stress reactivity. Subjects in the experimental group (n = 11) were exercise trained for eight weeks (25-30 min, 3 day.week^{-1}, 60-75% heart rate reserve), and then detrained for a further six to eight weeks. Heart rate and blood pressure response to mental arithmetic and forehead cold exposure and the carotid-cardiac vagal baroreflex after the training period were compared with responses after the detraining. The control group (n = 9) were matched on peak oxygen uptake and selected physiological and psychological factors that influence blood pressure and heart rate. The rationale of the study design was based upon the assumption that a six to eight week period of detraining is sufficient for the reversal of autonomic adaptations to exercise. Following an 11.5% decrease in $\dot{V}O_{2max}$ in the experimental group, after detraining, mean arterial blood pressure response to the mental arithmetic task, and systolic blood pressure response during cold head exposure were both elevated. However, despite higher submaximal exercise heart rates after detraining, the experimental group showed no change in the carotid-cardiac vagal baroreflex, or heart rate response to the autonomic challenges. The lack of significant findings may be due to the length of training period employed - Raven and Pawelczyk (1993) have suggested that cardiovascular adaptations associated with exercise training take far longer than an eight to ten week training period, which is commonly reported in the literature. The other notable finding was that resting blood pressure was significantly elevated after detraining in the experimental group [systolic blood pressure (SBP): 113 ± 8.9 to 121.2 ± 9.0 mmHg; diastolic blood pressure (DBP): 63.0 ± 8.4 to 68.3 ± 6.8 mmHg). None of the above changes occurred in the sedentary matched control subjects. The authors suggested that the increases in SBP

response during cold head exposure, after detraining, were possibly due to a strong β-adrenergic activation, implying that the mechanisms involved in the stress reactivity lowering effects of exercise may be more strongly β-adrenergically mediated. However, van Doornen, de Geus, and Orlebeke (1988) suggested that heart rate reactivity and catecholamine release might not be as important as the resulting effects on net cardiac and vascular responses. Using a tone-avoidance reaction time task, van Doornen and de Geus (1989) showed that endurance athletes were distinguished from sedentary subjects mainly by a smaller increase in peripheral vascular resistance in response to stress, and to a lesser extent by a reduced cardiac response. Thus, there is a need to examine the effects of fitness and exercise on the specific cardiovascular patterning responses to stressors in offspring hypertensives, because previous research has focused on gross measures of heart rate and blood pressure reactivity. Also, measuring autonomic balance of the responses is vital to understand the potential mechanisms.

In summary, there is emerging evidence to suggest that fitness and physical activity may decrease stress reactivity, thus decreasing the risk of hypertension among normotensive individuals who are already at risk because of familial history of hypertension.

2.2.3 Coping Mechanisms and Personality

A possible further point to consider in looking at the interaction of stress, lifestyle, and hypertension development is how personality factors are involved with an individuals ability to cope with stress. Beilin (1997) has suggested that the relationship between stress and blood pressure might be mediated or confounded by coping mechanisms influencing lifestyle factors known to directly affect blood pressure (see Figure 2.2). Beilin's research involved an assessment of work stress,

identification of coping strategies, details of lifestyle factors (obesity level, drinking, smoking, exercise, dietary habits), and resting blood pressure measures in 654 male and female subjects at a government workplace. The main findings demonstrated no direct association between measures of work stress and blood pressure but both body mass index and lifestyle factors were the major contributors to blood pressure levels in men and women. Also, five adaptive and maladaptive coping mechanisms were identified which were likely to be either beneficial or deleterious to physical or mental health. These coping mechanisms were independently related to both job stress and blood pressure levels. Maladaptive coping behaviours reported in response to stress were in the form of excessive drinking, excessive consumption of foodstuffs and/or cigarettes, and avoidance or denial of stressful work situations.

Miller, Dolgoy, Friese, and Sita (1998) have also shown that personality and family history of hypertension moderate the cardiovascular stress reactivity response. They showed that offspring hypertensives that were classed as 'high hostile' displayed a significantly higher level of cardiovascular reactivity to an 'harassment stressor' compared with offspring hypertensives that were 'low hostile' and controls that were high and low hostile. Miller *et al.* also reported that hostile subjects reported an anger-expression style that is a tendency to hold anger in, which has also been linked to the hypertensive disease process (Diamond, 1982).

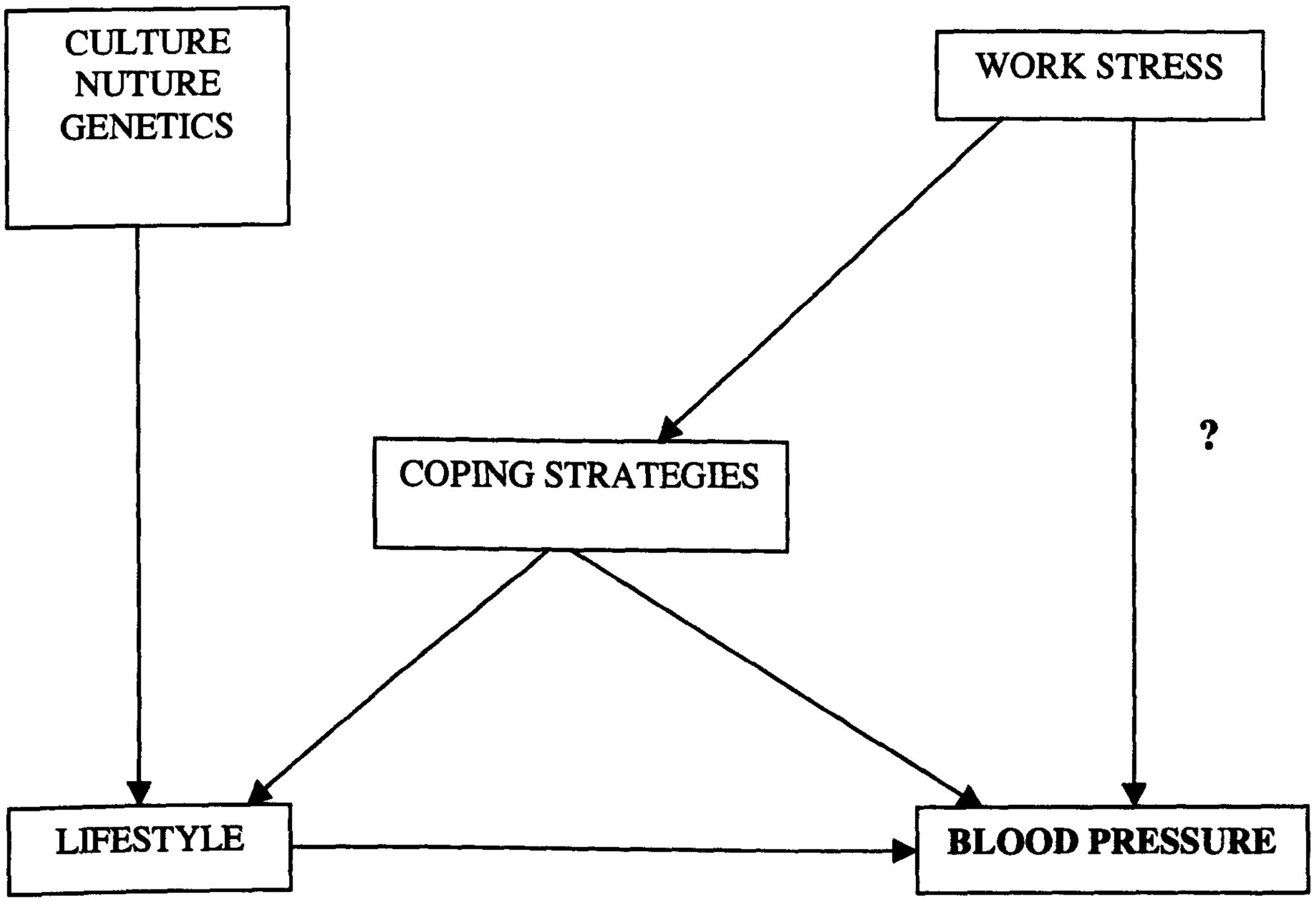


Figure 2.2. A conceptual model to illustrate the relationship between work stress, coping, lifestyle, and hypertension (Beilin, 1997).

2.3 Anti-hypertensive/ Stress Reactivity Lowering Mechanisms of Exercise

There is a strong body of evidence to support the anti-hypertensive effects of exercise (see Chapter 1), and also the role of exercise in reducing stress reactivity, which may play a role in lowering risk of hypertension. However, the mechanisms underlying these effects are largely unknown, and probably multi-factoral. The effects of acute exercise may be related to different mechanisms compared with chronic training adaptations. At the onset of exercise substantial cardiovascular adjustments are needed in order to sustain an exercise bout. These adjustments are primarily to increase metabolism in the contracting muscle and focus on increasing oxygen delivery. This is achieved in part by increasing cardiac output and by pronounced dilatation in the vasculature of exercising skeletal muscle. There are several important physiological changes resulting from a bout of acute exercise that may be linked to hypotensive and stress reactivity lowering mechanisms. These include increases in the catecholamines and other hormones such as growth hormone and cortisol; increases in chemical by-products, such as lactate, adenosine, potassium; increases in carbon dioxide and reduced oxygen; increases in temperature. This is in contrast to chronic training adaptations where mechanisms are related to long term structural changes such as vascular capillarisation, cardiac adaptations, changes in lipid profiles, changes in hormone balance, and so forth.

A mechanism that reduces blood pressure must be integrally involved with the control of total peripheral resistance and/or cardiac output, although research is equivocal. For example, a number of researchers have demonstrated that antihypertensive effects of exercise are related to a post-exercise fall in myocardial performance (Bennett, Wilcox, & Macdonald, 1984; Hagberg, Montain, & Martin, 1987), whereas others have suggested that reductions in peripheral vascular resistance

are responsible (Cleroux, Kouame, Nadeau, Coulombe, & LaCourciere, 1992a, 1992b; West *et al.*, 1998). It is likely that a mechanism involved in both the anti-hypertensive and stress reactivity lowering effects of exercise is closely related to SNA. There are currently a number of mechanisms that have been proposed (for review see Tipton, 1991) which include autonomic, metabolic, electrolyte and renal, and myocardial and vessel structural mechanisms.

2.3.1 Autonomic Mechanisms

Longitudinal studies (Duncan *et al.*, 1985; Jennings *et al.*, 1986; Meredith *et al.*, 1991; Urata *et al.*, 1987) that have employed plasma catecholamine concentration as an index of SNA have consistently shown that endurance training reduces plasma norepinephrine concentration. Jennings *et al.* (1986) observed a 65% reduction in norepinephrine spillover rate in 10 out of 12 subjects who exercised 40 min, 7 day.week^{-1}, 4 weeks, and a decrease in resting peripheral vascular resistance. Duncan *et al.* (1985) trained subjects for 16 weeks, 60 min, 3 day.week^{-1}, and reported that hypertensive patients with elevated baseline plasma catecholamine levels had greater reductions in blood pressures after exercise training than did patients with normal catecholamine levels. Furthermore, Urata *et al.* (1987), using a training intervention of 65 min, 3 day.week^{-1}, 10 weeks, found a significant correlation between changes in plasma norepinephrine and changes in mean blood pressure ($r = 0.69$, $P < 0.05$). However, because plasma catecholamine levels represent a measure of average sympathetic neural activity, it is difficult to determine whether central, peripheral, or local mechanisms are primarily or secondarily responsible for the changes. That a reduction in blood pressure, through training, was observed before any reductions in plasma norepinephrine (Jennings *et al.*, 1986), suggests that a central mechanism may not influence the initial fall in blood pressure. Although there is no evidence to

suggest the possibility of down regulation of adrenergic receptors after chronic exercise training in humans, results from animal studies show that after an acute bout of exercise vascular responsiveness was reduced (Howard & DiCarlo, 1992). Using vasoactive agonists infused into the hindlimb of the conscious rabbit, blood flow responses in the isolated hindlimb were markedly reduced following a bout of treadmill exercise to exhaustion. The authors suggested that this might be due to an exercise-induced down regulation of α and/or β-adrenergic receptors. Since it has been suggested that offspring hypertensives are hyper-reactive in the β-adrenergic pathways during stress, then a down regulation of these receptors may be a possible mechanism in a stress reactivity lowering effect of exercise.

2.3.2 Baroreceptor Function

The sensitivity and functioning of the baroreceptors are integrally involved with the SNS. Therefore, as the baroreceptors have already been identified as a mechanism for heightened SNA in offspring hypertensives, alterations to baroreceptor control through exercise training may be a key mechanism. Evidence regarding the effects of exercise training on cardiac (arterial) baroreceptor control is conflicting; in some studies baroreflex control is enhanced by training in normals (McDonald, Sanfilippo, & Savard, 1993), and in borderline hypertensive patients (Somers, Conway, Johnston, & Sleight, 1991), but in other studies it was unchanged (Buckworth *et al.*, 1997; Lightfoot, Claytor, Torok, Journell, & Fortney, 1989; Seals & Chase, 1989), or depressed (Bedford & Tipton, 1987; Smith, Graitzer, Hudson, & Raven, 1988). However, these studies were limited to the baroreceptor reflex ability to change heart rate via vagal and sympathetic modulation of the sinus node. Grassi, Seravalle, Calhoun, and Mancia, (1994) studied the effect of physical training on baroreceptor control of sympathetic nerve traffic and heart rate in healthy, young

normotensive humans. Postganglionic MSNA and heart rate were measured during intravenous infusion of vasoactive drugs in order to estimate baroreceptor sensitivity. The measurements were taken from the experimental group ($n = 9$) before and after a 10-week endurance exercise training intervention (2 hr, 5 day.week^{-1}) consisting of long distance running, and also from sedentary control subjects ($n = 4$). The training resulted in an increased $\dot{V}O_{2max}$, from 34.8 ± 2.1 ml.kg^{-1}.min^{-1} to 40.4 ± 1.8 ml.kg^{-1}.min^{-1}, significantly reduced mean arterial blood pressure (97.5 ± 1.8 to 86.5 ± 2.6 mmHg, $P < 0.05$), and MSNA (21.2 ± 2.3 to 14.0 ± 1.8 bursts.min^{-1}). Also, mean blood pressure increases, induced by phenylephrine infusion, caused significantly greater reductions in MSNA, but not heart rate, after training. Furthermore, mean blood pressure decreases induced by nitroprusside infusion caused significantly greater increases in MSNA and heart rate after training. No changes occurred in the age-matched sedentary controls. From these findings, the authors suggested that the reduction in SNA originates from a central effect of training. This is because the reduction in plasma norepinephrine induced by training is not accounted for by factors attenuating the release of this substance from nerve terminals, but by an actual reduction in neural sympathetic discharge. Also, because the training intervention seemed to predominantly influence MSNA, and in light of previous evidence, the authors concluded that the effects of physical training on the baroreceptor control of the systemic circulation, via the SNS, may be different from the concomitant effect of training on baroreceptor control of cardiac sympathetic activity.

The C-P baroreceptors are integrally involved with the control of the systemic circulation, and evidence regarding the effects of endurance training on these baroreceptors is equally equivocal. Using mild levels of lower body negative pressure (LBNP) (0 to -20 mmHg) to selectively 'unload' the C-P baroreceptors, a number of

researchers have found that moderate intensity endurance training attenuates the C-P baroreflex control of skeletal muscle vascular resistance, both in hypertensive subjects (Kouamé, Nadeau, Lacourciere, & Cleroux, 1995), and in normal subjects (Mack, Thompson, Doerr, Nadel, & Convertino 1991; Seals & Chase, 1989; Stevens, Foresman, Shi, Stern, & Raven, 1992), whereas others have found it to be unchanged (Lightfoot *et al.*, 1989; McDonald *et al.*, 1993). Furthermore, when employing a low intensity training intervention some have found an augmented baroreflex response, in hypertensives (Jingu *et al.*, 1988), and also an unchanged response (Kouamé *et al.*, 1995). It is quite clear that training intensity is an important factor, but other inconsistencies may be related to the frequency and length of the overall training period. It is noticeable that the authors who reported an attenuated baroreflex all employed training interventions of 20-30 weeks [with the exception of Mack *et al.* (1991) who used a 10-week programme], whereas those who found no change used a shorter 10-week programme. Furthermore, Lightfoot *et al.* (1989) suggested that differences in the methods used to measure C-P baroreceptor functioning may have been responsible for the discrepancies; a number of authors have used an "incremental" LBNP protocol, which provides sequential increases in LBNP exposure (Lightfoot *et al.*, 1989; Mack *et al.*, 1991; Stevens *et al.*, 1992), whereas others have used "jump" protocols, where the negative pressure stages are separated by periods of no pressure (Kouamé *et al.*, 1995; Seals & Chase, 1989). The discrepancy between "jump" and "incremental" protocols may be in the amount of fluid that is pooled, as suggested by Wolthuis, Hoffler, and Johnson (1970). However, in light of these assertions there seems to be no clear consistency between the type of protocol used and the effects of training on the baroreflex functioning. A further methodological discrepancy in this area is the importance of relating the forearm vasoconstrictor

response to the physiological stimulus of C-P baroreflex unloading (i.e., central venous pressure), as opposed to the level of LBNP.

From the findings that have suggested an attenuated C-P baroreflex response after training, it is interesting to speculate on the potential mechanism. A number of mechanisms have been implicated: 1) a possible resetting of the C-P baroreceptor's operational point, 2) alterations at the afferent level, central integration level, and at the efferent level. There is no evidence to support a resetting process because the baseline level of the reflexly changed variables (mean arterial pressure, forearm vascular resistance, and changes in estimated central venous pressure during LBNP) remain similar before and after training. Thus, the mechanism is most likely related to alterations in the cardiovascular reflex arc. Two studies (Mack *et al.*, 1991; Stevens *et al.*, 1992) have associated the reduction in C-P baroreflex sensitivity with an exercise induced hypervolemia, and thus have suggested that a mechanism may be related to an interaction between reflexes that regulate intravascular volume and baroreflexes that regulate vascular resistance. There is also evidence to suggest that structural changes to the cardiovascular system may be integrally involved. For example, Levine, Buckley, and Fritsch (1991) reported that maximal calf conductance was a strong independent predictor of LBNP tolerance. However, Kouamé *et al.* (1995) reported that a decreased C-P baroreflex response after training was not related to a mechanism pertaining to hypervolemia, as blood volume was not modified in their subjects after training. Also, plasma norepinephrine levels during LBNP stimulation were similar before and after training, suggesting that efferent sympathetic nervous activity was not modified. Instead, they suggested that the reduced forearm vascular resistance response was related to alterations at the effector organ level, that is the vascular smooth muscle. That the minimal vascular resistance in the forearm after

training was unchanged suggests that the structure of the vessels was unaffected during the short 10-week training period and therefore alterations to the α-adrenergic receptors were implicated. A training induced alteration of α-receptor function was also supported by Stevens *et al.* (1992), who found that after training subjects elicited an average 4 mmHg decrease in DBP during LBNP, whilst before training DBP increased by 2 mmHg during LBNP. Thus, it seems likely that the mechanism may be multifactorial, and involve adaptations at the afferent, central, and efferent levels of the reflex arc, dependent on the length and intensity of the exercise stimulus.

2.3.3 Renal Depressor Mechanisms

Due to the disturbed renal hemodynamics and handling of sodium that is often associated with hypertension a number of researchers have investigated the effect of exercise training on renal functioning in hypertensive patients (Kinoshita *et al.*, 1991; Kohno *et al.*, 1997; Sakai *et al.*, 1998). Kohno *et al.* (1997) evaluated 24 hr blood pressure, glomerular filtration rate, renal blood flow, filtration fraction, plasma renin, aldosterone, norepinephrine activity, and fractional excretion of sodium in subjects with mild to moderate hypertension before and after a three week exercise training programme (four 6-min sessions daily at 75% $\dot{V}O_{2max}$). After the training period subjects were then classified as responders (those with significantly reduced 24 hr blood pressure) and non-responders (those who had not reduced blood pressure). Before training the responders had significantly higher renal vascular resistance, plasma renin and aldosterone activity, and lower fractional excretion of sodium than non-responders, suggesting a more activated renin-aldosterone system with higher renal artery tone in responders. However, with exercise the responders' renin angiotensin system and sympathetic nervous system were suppressed (significant reductions in plasma renin and norepinephrine activity), resulting in a reduced renal

vascular resistance and filtration fraction. Fractional excretion of sodium was also increased in responders, although this was not significant. That there was no significant reduction in resting heart rate after training suggests the blood pressure lowering mechanism may have been related to reductions in vascular resistance. Indeed, significant correlations between change in mean arterial pressure and the changes in filtration fraction and renal vascular resistance suggests that the specific mechanism may be linked with a reduction in renal vascular resistance through a reduction in regional sympathetic activity. These findings are in agreement with Meredith *et al.* (1991) who showed that after 4 weeks of exercise training (40 min, 3 day.week^{-1}, 60-70% $\dot{V}O_{2max}$) a fall in blood pressure was mainly explained by a 41% decrease in renal norepinephrine spillover and an increase in renal vascular conductance of 10%. They also found no change in cardiac norepinephrine spillover rate. Thus, the findings of Kohno *et al.* provide evidence to suggest that exercise may be more beneficial in lowering blood pressure in hypertensives with higher renal vascular resistance.

Further studies have focused on the role of plasma volume depletion mechanisms. These mechanisms are thought to promote natriuresis and diuresis by inducing sodium excretion. There are a number of potential hormones and other factors that may be involved with this process. These include atrial natriuretic peptide (ANP) that is released from the cardiac atria when the extra cellular fluid volume is expanded. The primary action of ANP is to inhibit sodium re-absorption in the distal parts of the nephron, thus increasing sodium excretion in the urine. ANP also acts on two other sodium conserving mechanisms that include inhibiting renin secretion in the kidney and aldosterone secretion from the adrenal cortex. ANP is also thought to inhibit SNA thus decreasing renal vascular resistance. Tanaka *et al.* (1986) showed

that ANP levels increased during acute exercise in young healthy volunteers. However, Kinoshita *et al.* (1991) did not find any increase in plasma ANP factor levels at rest after 10 weeks of mild (lactic threshold) exercise in middle aged hypertensives. That Kinoshita found a correlation between decrease in ANP with both decrease in SBP ($r = 0.56$, $P<0.05$) and 24 hr urinary sodium excretion ($r = 0.64$, $P<0.05$) suggests other factors promoting natriuresis may be involved. Other factors that may be involved include the dopamine system and taurine, which are both found to be suppressed in hypertensives (Lee, 1981; Ogawa, Takahara, Ishijima, & Tazaki, 1985). Kinoshita *et al.* (1991) and Sakai *et al.* (1998) both observed increases in urinary dopamine excretion in hypertensives after 4 weeks of exercise training, which was significantly correlated with decrease in blood pressure and urinary sodium excretion. Tanabe *et al.* (1989) showed that mild exercise for 10 weeks in hypertensives increased serum taurine concentration by 26%, which was correlated to a decrease in plasma norepinephrine. Thus, there is a body of evidence to support the role of exercise in a blood pressure reducing mechanism that relates to changes in renal function. However, more causal evidence is needed to implicate the role of specific factors in renal depressor mechanisms because previous studies have only provided correlations. Also, when looking at renal blood pressure lowering mechanisms it is important to still consider not just peripheral mechanisms but also central adaptations. For example, Sakai *et al.* (1998) stated that a post-exercise natriuresis effect was the main cause for lower blood pressure despite their findings of a significantly reduced cardiac index.

2.4 Summary

In summary, the present literature suggests that the interaction of genetic pre-disposition and the environment are integrally involved with the early development of

hypertension. In particular, heightened cardiovascular reactivity to psychological stress has been identified as a key marker for the future development of hypertension. The sympathetic nervous system seems to be involved with heightened cardiovascular reactivity in offspring hypertensives and may also be involved with an exercise induced reactivity lowering effect.

CHAPTER 3

METHODOLOGY

3.1 Overview

Three studies were designed in order to investigate the effects of physical activity and acute exercise on risk markers of hypertension in offspring hypertensives. For Studies I and II a cross-sectional design was employed for which highly and moderately active male offspring hypertensives were recruited. This design was adapted from Buckworth *et al.* (1994) who were also interested in the effects of physical activity and fitness on autonomic responses in offspring hypertensives. The decision was made not to employ a control group of subjects without family history of hypertension because: 1) previous research has already documented cardiovascular reactivity patterns using offspring hypertensives compared with offspring normotensives and clearly demonstrated a strong effect for family history of hypertension; 2) a certain proportion of the population may unknowingly suffer from undiagnosed hypertension, which may produce a number of false negative offspring hypertensive subjects in the control group contributing to a type II error. In Study III an exercise intervention strategy was used with moderately active male offspring hypertensives where subjects acted as their own control.

In Study I the relationship between physical activity level and cardiovascular function during a number of physical and mental stressors was assessed. In Study II cardiovascular reactivity and renal responses to mental challenge were investigated. Then, in Study III the effect of acute exercise on cardiovascular reactivity to mental challenge was examined. The design employed in the final study allowed a possible causal relationship between acute exercise and stress reactivity to be determined.

In all studies the cardiac variables stroke volume and cardiac output were assessed using impedance cardiography, whereas heart rate was assessed using electrocardiography. Blood pressure was measured on a beat-to-beat basis using an Omeda Finapres blood pressure monitor. Forearm blood flow was assessed using Hokanson Plethysmography with the venous occlusion technique. Maximal oxygen uptake was assessed using the Douglas bag collection method. In Study II urinary sodium and potassium were measured using a flame photometer and creatinine using a spectrophotometer.

3.2 Subjects

Subjects were considered suitable for participation in the study if the following criteria were met: male; aged 18-30 years; general good health; normotensive blood pressure (systolic blood pressure (SBP) below 140 mmHg, diastolic blood pressure (DBP) below 90 mmHg); and a family history of hypertension. Family history of hypertension was defined as having biological parents or grandparents diagnosed with essential hypertension (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg). The researcher was confident as to the reliability of reports on family history of hypertension because previous research has demonstrated that adolescents were able to report accurately on the hypertensive status of their family (Matthews, Manuck, & Saab, 1986).

3.2.1 Sample Size

On the basis of prior research in aerobic fitness and reactivity to psychosocial stressors, meta-analysis work by Crews and Landers (1987) has suggested medium sized effects of 0.5. Effect size has been defined as the difference in means between groups (M_1- M_2) divided by the standard deviation (*SD*) (Cohen, 1969).

$$ES = (M_1 - M_2) / SD$$

However, recent research comparing stress reactivity responses in offspring hypertensives with offspring normotensives has produced larger effect sizes of 0.9 (Anderson *et al.*, 1987). A recommended appropriate power in behavioural research is 0.8 (Green, 1991). Thus, based on a large effect size, sample sizes of 10-12 subjects per group for Studies I and II would provide a statistical power of 0.8 at an α of $P <$ 0.05 (Thomas & Nelson, 1996). Recent research examining the effects of acute exercise on cardiovascular responses have shown moderate effects of 0.6 for blood pressure response in normal healthy subjects (Steptoe *et al.*, 1993). Thus based on this effect size a sample size of 12-15 subjects would be required to complete both control and exercise conditions in Study III.

3.3 Equipment and Measures

3.3.1 Subject Screening

3.3.1.1 Informed consent. Subjects recruited for the study all signed written informed consent that was approved by the University human ethics committee (Appendix IA) and all subjects were provided with information concerning experimental procedures (Appendix IB, IIA, IIIA).

3.3.1.2 Health questionnaires. Subjects were administered a medical history questionnaire (Appendix IC) and the Physical Activity Readiness Questionnaire (Appendix ID).

3.3.1.3 Psychological state. To account for the potential influence of anxiety on autonomic responsiveness, the State-Trait Anxiety Inventory Form X-1 (STAI: Spielberger, Gorsuch, & Lushene, 1970) was administered (Appendix IE).

3.3.1.4 Physical activity and fitness. Levels of physical activity were estimated ($kcal.kg^{-1}.d^{-1}$) through a semi-structured interview, using the seven-day Physical Activity Recall (PAR: Sallis, Haskell, & Wood, 1985) – Appendix IF. The PAR is

designed to include a variety of physical activities, but only those of moderate intensity and greater are counted. Dishman and Steinhardt (1988) established reliability and concurrent validity for the PAR; using 163 college students, a significant relationship between the first test and a nine week re-test was obtained (r = 0.42). Also, using 24 male students, a significant relationship between the 7-day PAR and past year activity questionnaire (r = 0.83) and maximum oxygen consumption (r = 0.61) was found.

Cardiorespiratory fitness was assessed through a maximal oxygen uptake ($\dot{V}O_{2max}$) test using Douglas bags for the collection of gases. Gases were analysed using a zirconia oxide O_2 analyzer, and an infra-red CO_2 analyzer. Subjects exercised in the upright position on a stationary electronic ergometer (Excalibur Sport) at a cadence of 70 rpm until volitional exhaustion. The initial load was 30 W for the first 2-min and was increased incrementally by 1 W every 2 s thereafter. $\dot{V}O_{2max}$ was determined as the highest 15 s average oxygen consumption in $l.min^{-1}$. The end point was achieved when the subject was unable to continue. Other indicators included heart rate at age-estimated maximum, plateau of oxygen consumption, and a respiratory exchange ratio greater than 1.10.

3.3.1.5 Physical measures. Body height and weight were measured with subjects wearing only light clothes without shoes. Skin folds were measured from four sites using callipers, and body fat calculated from the Durnin and Wormsley (1974) formula. Baseline blood pressure was measured after a 10-min period of supine rest, taken at the left brachial artery by the auscultatory method using a mercury sphygmanometer.

$$SV = rho.(L/Z_0).\ LVET.\ dZ/dT\ max$$

Where:

SV = stroke volume

rho = resistivity of blood (135 $ohm.sec^{-1}$)

L = distance between voltage electrode (cm)

Z_0 = basal impedance[1]

LVET = left ventricular ejection time

dZ/dT max = maximum rate of change of impedance during cardiac systole ($ohm.sec^{-1}$).

---

[1] The value of Z_0 influences the height of the dZ/dT signal such that subjects with lower Z_0 values have smaller dZ/dT deflections. Thus, the inclusion of Z_0 in the denominator of the stroke volume equation normalizes its effect on dZ/dT.

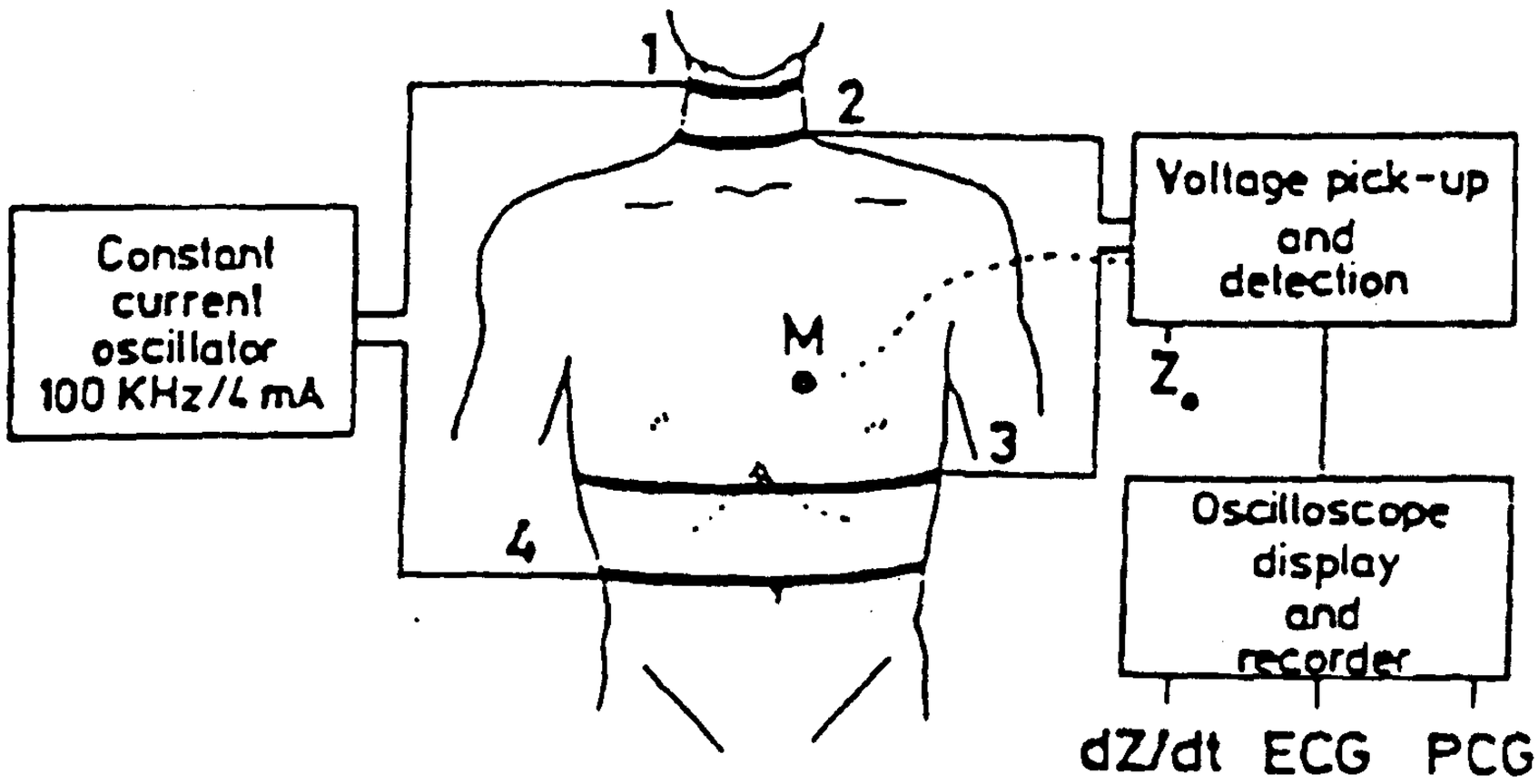


Figure 3.1 Tetrapolar configuration of aluminium electrodes used in impedance cardiography. The two inner electrodes (2 and 3) were measured and entered into Kubicek (1970) equation to calculate stroke volume.

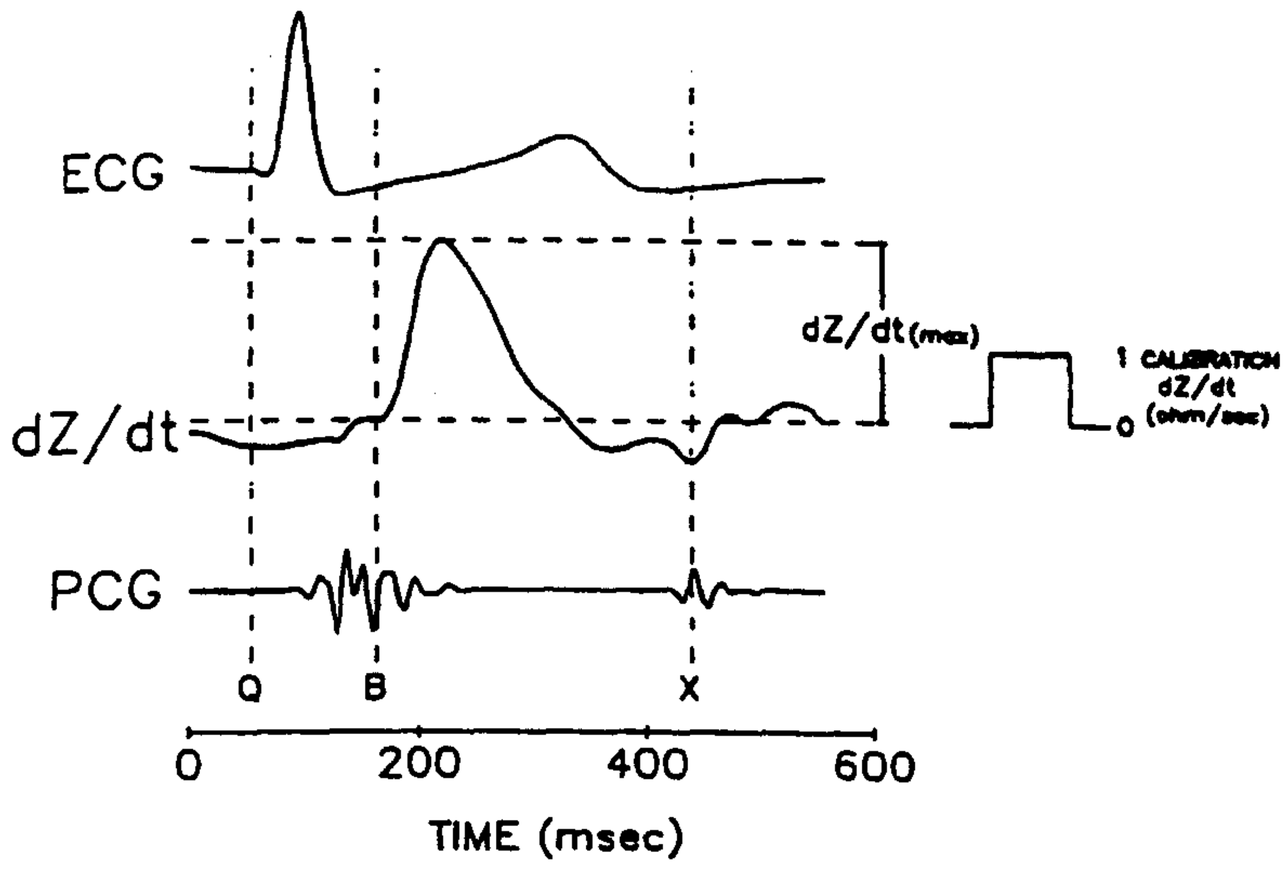


Figure 3.2. Impedance cardiogram waveform components shown are the ECG Q-wave (Q), dZ/dT B-point (B), and dZ/dT X-point (X). Electrocardiogram (ECG), first derivative of the pulsatile thoracic impedance signal (dZ/dT), and phonocardiogram (PCG) recorded during electromechanical systole of cardiac cycle (from Sherwood *et al.*, 1990). The B-point occurs immediately after the aortic valve opens and the X-point coincides with the closing of the aortic and pulmonary valves.

There are three main assumptions that underlie the derivation of the impedance SV equation. First, the decrease in impedance during systole is due to a change in aortic blood volume; second, the thorax is a cylindrical conductor composed of two parallel conducting paths, one path through the tissues and the other through the blood; third, there is no significant arterial run off from the thorax during systole. Most investigators agree that dZ/dT is primarily the result of the ejection of blood from the left ventricle, however it is unclear whether this change in impedance is solely due to a change in aortic blood volume. Lamberts, Visser, and Zijlstra (1984) have demonstrated that 60% of dZ/dT is generated by the velocity of the ejected blood. This velocity-dependent change in blood resistivity as reflected in dZ/dT is possibly related to the reorientation of erythrocytes as blood begins to flow (Lamberts *et al.,* 1984). The second assumption relating to the thorax being modelled as a cylindrical conductor has been tested by Visser, Lamberts, and Zijlstra (1987) in a series of experiments involving exchange transfusion with stroma-free hemoglobin. The findings of Visser *et al.* (1987) suggest that this aspect of the SV equation is valid. However, the final assumption that there is no significant arterial run off from the thorax during systole is problematic because blood continues to flow into and out of the thorax throughout the cardiac cycle. This particular aspect of the SV equation has not been fully evaluated.

In an attempt to validate impedance cardiography, the measurement of CO during rest, using impedance, has been compared with other methods to assess CO, such as thermodilution technique (Donovan, Dobb, Woods, & Hockings, 1986), M-mode echocardiography (Aust, Belz, Belz, & Koch, 1982), Doppler ultrasound (Barbacki, Gluck & Sandhage, 1981), left ventriculography (Ebert, Eckberg, Vetrovec, & Cowley, 1984), electromagnetic flow probe (Ehlert & Schmidt, 1982),

direct Fick (Miles *et al.*, 1988), dye dilution (Milsom, Forssman, Biber, Dottori, & Silvertsson, 1983), isotope dilution (Williams & Caird, 1980), and radionuclide angiocardiography (Williams & Caird, 1985). The correlation between impedance cardiography and other methods has generally been greater than 0.70, showing that this is a valid measure of CO. The Minnesota impedance cardiograph, used in the present study, was compared during exercise against carbon dioxide re-breathing and found to be valid (McLaren, 1995). The method was also found to be reliable [r = 0.98; p<0.01, two measurements on two different occasions in six subjects (McLaren, 1995)]. Thus, the majority of investigators agree that the impedance technique can accurately track the magnitude and direction of changes in CO. Although some controversy exists on whether the absolute values are accurate, a review of studies evaluating impedance cardiography (Miles and Gotshall, 1989) demonstrated that 14 of the 18 studies supported the accuracy of the impedance technique. Miles and Gotshall (1989) suggested that CO measured by impedance at rest is usually within ± 15% of the more standard invasive techniques.

The close correlation of the impedance technique with other techniques for estimating SV suggests that the assumption of no arterial run-off does not normally present significant error and may only be problematic in circumstances when the ejection pattern is altered (e.g., valvular disease, heart failure). Several improvements in the methodology of impedance measures have been proposed that include a modified SV equation (Bernstein, 1986) that takes into account the morphology of the subjects and reduces the effect of changes in Z_0 on the calculation. Also, in order to reduce the effect of respiration on the dZ/dT a short period of apnea is frequently employed. However, the development of ensemble-averaging that is designed to

cancel out non-periodic waveforms such as respiratory-induced baseline shifts, motion artefacts, and electrical noise was employed in the present study.

3.3.2.3 Blood pressure. Blood pressure was monitored on a beat-to-beat basis using a 2300 Finapres blood pressure monitor (Ohmeda Monitoring Systems) with the pressure cuff placed on the middle finger of the subject's left hand maintained at heart level. Beat-to-beat blood pressure measures from the Finapres have been validated against simultaneous intra-arterial monitoring (Parati, Casadei, Groppelli, Di Rienzo, & Mancia, 1989).

3.3.2.4 Heart period variability. Parasympathetic influence on the heart was assessed through time series analysis of heart period variability (HPV_{ts}) in the high frequency (0.12 – 0.4 Hz) and medium frequency (0.07 – 0.11 Hz) domain using the Mxedit software package (Delta-Biometrics, Inc, Bethesda, MD). Time-based data was converted from inter-beat-intervals (IBIs) by sampling successive 200 ms intervals. IBIs were plotted and edited to remove and interpolate artefact and outlying values. A band pass filter was used in order to remove sources of variance below the two major oscillatory heart rate spectral components. One of these components, termed high frequency, typically occurs at frequencies of 0.12 Hz and above, and the other, termed medium frequency, typically occurs at frequencies of 0.10 Hz and below. The natural logarithm of the band-passed variance (in ms^2) were then calculated and used as high and medium frequency measures of HPV_{ts}. Thus, HPV_{ts} appear as a linear scale ranging from 0 (minimal HPV_{ts}) to 10 (maximal HPV_{ts}: Porges, 1985).

3.3.2.5 Data processing. ICG signals were processed using ensemble averaging to filter artefact from the ICG every 25 s, and cardiac cycle timing was verified from heart sounds recorded by a phonograph microphone (the

phoncardiogram). Each impedance wave was edited through the edit mode of the COP software (COP, Microtronics, Chapel Hill, NC). Blood pressure data was averaged every 25 s then entered through the blood pressure edit mode to enable mean arterial pressure (MAP) and total peripheral resistance (TPR) to be calculated.

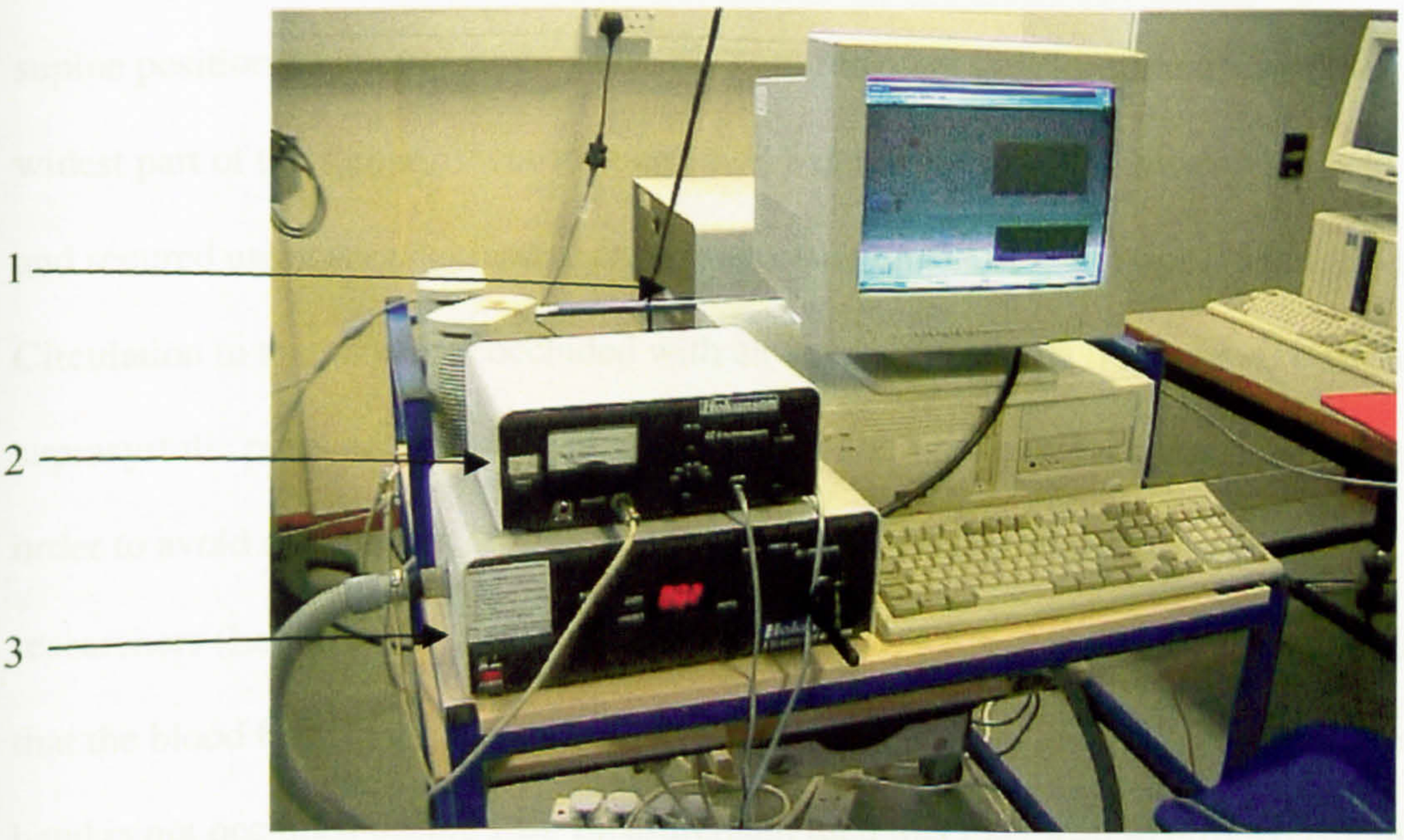
3.3.2.6 Derived measures. Heart rate (HR) was computed as the total number of IBIs (R-R interval) divided by the measuring time, expressed as $b.min^{-1}$. CO was computed by multiplying HR by SV, expressed as $l.min^{-1}$. Pre-ejection period (PEP) was computed as the interval from the ECG Q wave onset to the dZ/dT B point in ms (Sherwood *et al.*, 1990). Left ventricular ejection time (LVET) was computed as the interval from the dZ/dT B point to the dZ/dT X point in ms (Sherwood *et al.*, 1990). MAP was calculated using the COP software, using the equation 1/3 × pulse pressure [systolic blood pressure (SBP) – diastolic blood pressure (DBP)] + DBP. TPR was calculated from MAP/CO × 80, expressed as $dyne\text{-}s.cm^{-5}$. Rate pressure product (RPP), an indicant of myocardial oxygen consumption, was calculated as HR × SBP/ 100.

3.3.3 Blood Flow Measurement

Forearm blood flow (FBF) was measured using the venous occlusion technique. This technique is based on the principle that during venous occlusion the compression of the veins result in arterial swelling that result in changes in the arterial volume. At this time the rate of arterial inflow is measured. The change in circumference of the forearm, due to arterial inflow, is recorded as a change in electrical resistance of a mercury-in-silastic strain gauge placed around the forearm.

3.3.3.1 Plethysmography. Mercury in silastic-strain gauge plethysmography (Model EC-4, D.E. Hokanson, Inc, Bellevue, WA, USA) was used to measure FBF. A cuff inflator air source (AG101) and rapid cuff inflator (Model E20) were used to

inflate the venous occlusion cuffs (see Figure 3.3). The plethysmograph was interfaced with a Pentium PC to store the data generated by the Labview software (Version 4.0). Ten data points were recorded in Labview every second, which was later exported to Microsoft Excel software to perform further analysis.



Note: (1) inflator air source

(2) strain gauge Hokanson Plethysmograph

(3) rapid cuff inflator

Figure 3.3 Strain gauge Hokanson Plethysmograph with a cuff inflator air source (AG101) and rapid cuff inflator (Model E20).

3.3.3.2 Measurement procedures. Prior to data collection calibration was performed by attaching the selected strain gauge to the plethysmograph and then adjusting the voltage range so that it was between –1 and 1 V. With subjects in the supine position a mercury strain gauge (2-3 cm less than the circumference of the widest part of the forearm) was then attached 5 cm distal from the anticubical vein and secured using surgical tape to prevent any movement of the gauge (Figure 3.4). Circulation to the hand was occluded with an arterial wrist cuff (Hokanson) inflated to suprasystolic pressure (180 mmHg) at least 1 min before the measurement period in order to avoid disturbance of limb arterial inflow in the first minute. A number of researchers (Lenders, Janssen, Smits, & Thien, 1991; Williams, 1984) have suggested that the blood flow to the hand is mainly determined by skin blood flow, thus if the hand is not occluded during FBF measurement then this may lead to erroneously high values for forearm muscle blood flow. A venous occlusion cuff around the upper arm was then inflated to 50 mmHg for 5 of every 15 s providing one blood flow measurement every 15 s. The gradient of the blood flow wave was representative of change in forearm volume and thus arterial inflow (see Figure 3.5), which was calibrated for equivalent changes in voltage from the strain gauge. The blood flow was determined by calculating the gradient and intercept using a regression line formula that was programmed into Excel. The first second was disregarded to avoid errors from movement artefact. A minimum of six blood flow measurements was used to calculate average FBF for each block of measures. Forearm vascular resistance (FVR) was calculated by dividing MAP by FBF and forearm vascular conductance (FVC) by dividing FBF by MAP. FVR and FVC reflect changes to the radius of the vessel. FVC exhibits a linear relationship with flow whereas FVR is curvilinear.

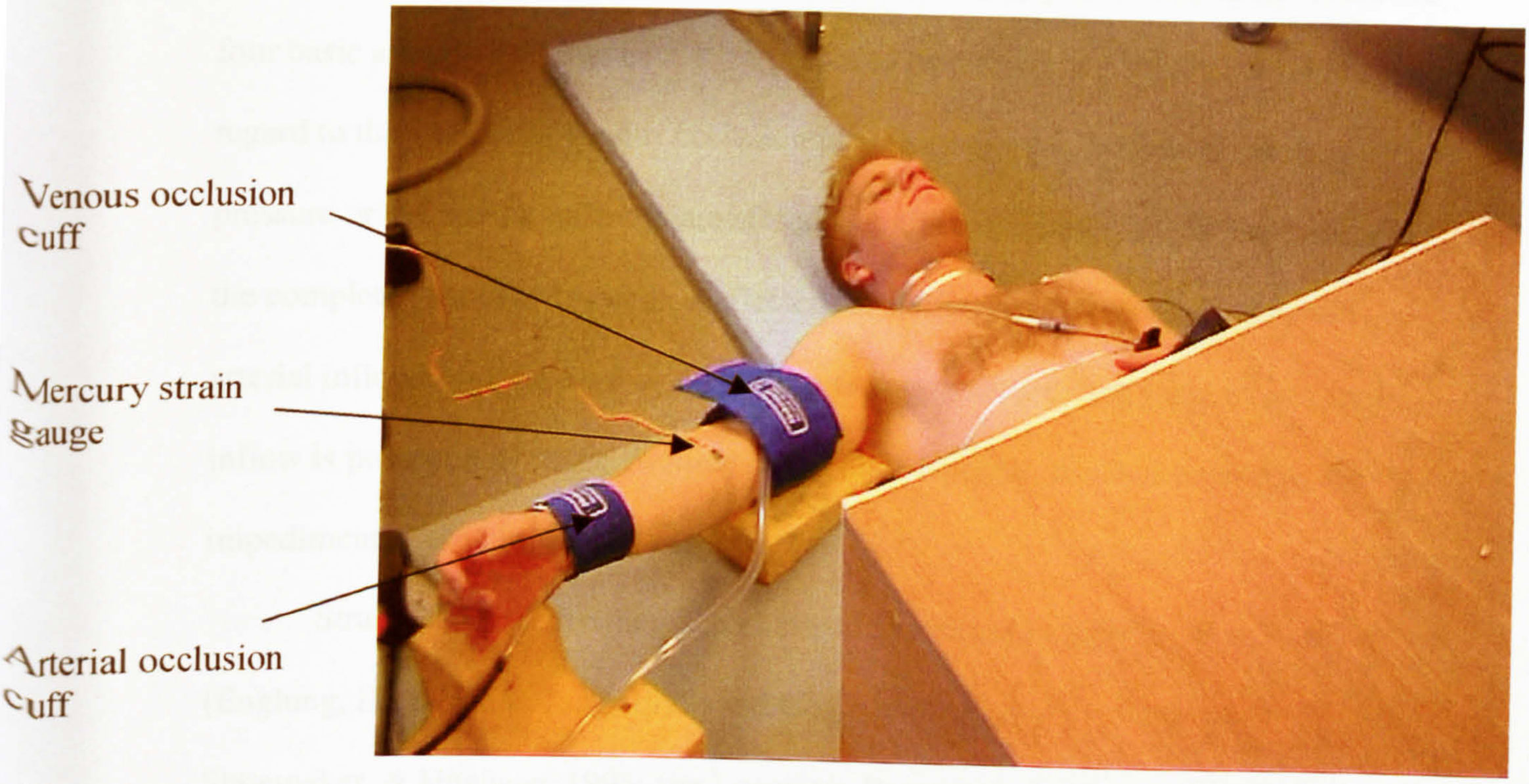


Figure 3.4. Placement of forearm strain gauge and cuffs.

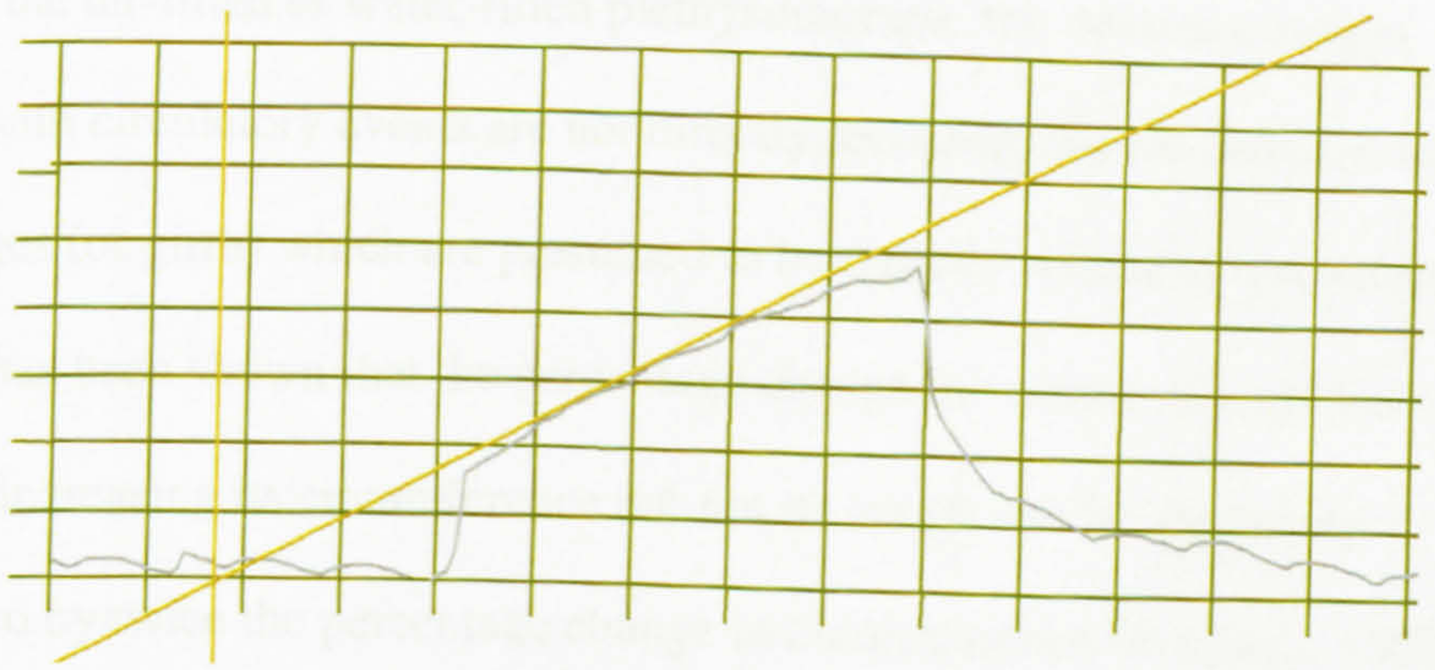


Figure 3.5. Measurement of forearm blood flow from the gradient of the blood flow wave.

3.3.3.3 Validity, reliability, and reproducibility of plethysmography. There are four basic assumptions that have been proposed by Formel and Doyle (1957) in regard to the validity of venous occlusion plethysmography. Firstly, the arterial pressure or the arterial inflow is not affected by the collecting (venous) cuff; secondly, the complete venous tamponade is effected for a finite period; thirdly, the rate of arterial inflow is not reduced by increasing venous pressure; lastly, the rate of arterial inflow is proportional to the swelling of the limb segment, which is caused by the impediment of the blood.

Strain gauge plethysmography has been validated against machine flow (Englung, Hallbook, & Ling, 1972) and Doppler ultrasound (Tschakovsky, Shoemaker, & Hughson, 1995; van Leeuwen, Barendsen, Lubbers, & De Pater, 1992). There is also fair agreement between water and strain gauge plethysmography (Clarke & Hellon, 1957; Whitney, 1953). The main criticism of the strain-gauge technique is that, unlike the air-filled or water-filled plethysmograph, the volume changes associated with circulatory events are not directly recorded, but are deduced from linear changes (or girth) which are presumed to be directly related to the volume changes. It has been shown that the percentage change in volume of a cylinder that enlarges by increasing its circumference but not its length can be accurately approximated by twice the percentage change in circumference (Whitney, 1953).

Strain gauge plethysmography has been found to be highly reproducible. Roberts, Tsao, and Breckenridge (1986) found that the coefficient of variation for the measurement of FBF in six subjects over six visits was 10.5%. Reproducibility studies performed with the strain gauge plethysmography equipment used in the present study (Nurhayati, 2001) showed that the coefficient of variation for FBF in six

males (aged 18-25years) measured both over consecutive and alternate days was 10.5%.

3.3.4 Urinary Measures

Urine samples were analysed for sodium and potassium using a flame photometer (Gallenkamp FGA-350-L). Sodium and potassium measures were corrected for urinary creatinine concentration and expressed as mmol.mgCr^{-1} because 24 hr urine collection was not carried out. Urinary creatinine concentration was measured based on the Jaffe reaction. A simplified technique was employed using a spectrophotometer to detect the difference in colour intensity measured at or near 500 nm before and after acidification, which is proportional to creatinine concentration (Heinegard & Tiderstrom, 1973).

3.4 Stressors

3.4.1 Lower Body Negative Pressure

The application of mild levels of lower body negative pressure (LBNP) was used to study the cardiopulmonary (C-P) baroreceptor control of FVR. LBNP was applied through the use of a LBNP chamber in order to unload the C-P baroreceptors through the reduction in central venous pressure (CVP), caused by a redistribution of central blood volume. Unloading of the C-P baroreceptors is thought to reduce inhibition of sympathetic outflow to the periphery, thus producing a vasoconstriction response. The chamber consisted of a box made of plywood, designed so that subjects' legs would be encapsulated up to the waistline, sealed at the iliac crest. A vacuum pump was sealed into the box in order to create negative pressures, which was measured using a digital pressure sensor (Sunx, Japan, model DP2-40E). The pressure sensor possesses repeatability of within 0.2%, and a response time of 2.5 ms or less. Reproducibility of pressure readings for a range of fixed power settings on the

vacuum pump with the chamber fully sealed at one end was examined. The mean coefficient of variation of pressure readings for four power settings performed on five separate occasions over a period of three months was 3.5%.

Changes in CVP are thought to reflect changes in venous return, which are detected by the C-P receptors. Thus, the slope of the linear relationship between change in FVR and change in CVP is commonly used as an index of cardiopulmonary baroreflex function, which is termed the cardiopulmonary slope (CPS). However, because a direct measure of CVP was not possible using the present experimental procedures, change in SV was used. The use of change in SV to indicate change in CVP assumes that the cardiac pressure-volume relationship (Starling curve) is linear over the range of pressure changes elicited by the present LBNP protocol. Reese (1991) evaluated the relationship between change in SV, measured by impedance cardiography, and change in CVP, estimated by measuring venous pressure changes in an arm vein in the lateral decubitus position, during 0 to -40 mmHg of LBNP. The results indicated a strong linear relationship ($r = 0.87$) between change in SV and estimated change in CVP. Therefore, for the purposes of present research the CPS was defined as the change in FVR divided by the change in SV ($\triangle$FVR/$\triangle$SV).

3.4.2 Stroop Word Colour Task

The Stroop is an active coping task (Stroop, 1935) which can be grouped with other tasks, such as mental arithmetic, as a cognitive stressor. Prior research has suggested that cognitive stress induces primarily β-adrenergic activity (Montoya, Brody, Beck, Veit, & Rau, 1997). The Stroop task consisted of a series of slides that were presented on a PowerPoint presentation, on a laptop computer. Each slide contained a word denoting a colour, such as RED, but the ink colour of each word

was printed in a different colour, such as PURPLE. Subjects were instructed to state the ink colour of each word. Slides appeared at a rate of one per second.

3.4.3 Forehead Cold Pressor Test

The forehead cold pressor has been shown to induce primarily α-adrenergic activity, resulting in a characteristic increase in TPR (Montoya *et al.*, 1997). In the present study, a leakproof gel refrigerant (BHD Laboratory Supplies, Dorset, UK) at a temperature of approximately 0°C was applied to the forehead.

CHAPTER 4

STUDY I. CARDIOVASCULAR RESPONSES TO PHYSICAL AND MENTAL STRESSORS IN HIGHLY AND MODERATELY ACTIVE MALES WITH A FAMILY HISTORY OF HYPERTENSION.

The aim of Study I was to conduct cross-sectional research using highly active and moderately active offspring hypertensives in order to identify differences in cardiovascular functioning between the groups during a number of tasks designed to activate the sympathetic nervous system (SNS). This firstly provided an opportunity to identify possible risk markers of hypertension, and secondly to formulate a rationale to conduct further research into the role of exercise in eliminating these markers. Based on previous research it was hypothesised that highly active offspring hypertensives would demonstrate reduced sympathetic outflow responses to orthostatic challenge and reduced cardiovascular reactivity to mental challenge, in comparison with their less active counterparts.

4.1 Protocol

Two groups were formed that comprised moderately active (MOD: <40 $kcal.kg^{-1}.d^{-1}$) and highly active male offspring hypertensives (HIGH: >40 $kcal.kg^{-1}.d^{-1}$). The HIGH group consisted of eight aerobically trained subjects engaged in daily aerobic physical activity, whereas the MOD group comprised of 10 subjects who were involved with recreational physical activities (e.g., soccer) no more than three times per week. The experimental procedures were performed in a laboratory at a constant room temperature of 24°C. All subjects were instructed to refrain from eating, smoking, and drinking alcohol or caffeine at least three hours before the experiment. All subjects were first screened, then prepared for the experiment, and sealed in the lower body negative pressure (LBNP) chamber (see Figure 4.1).

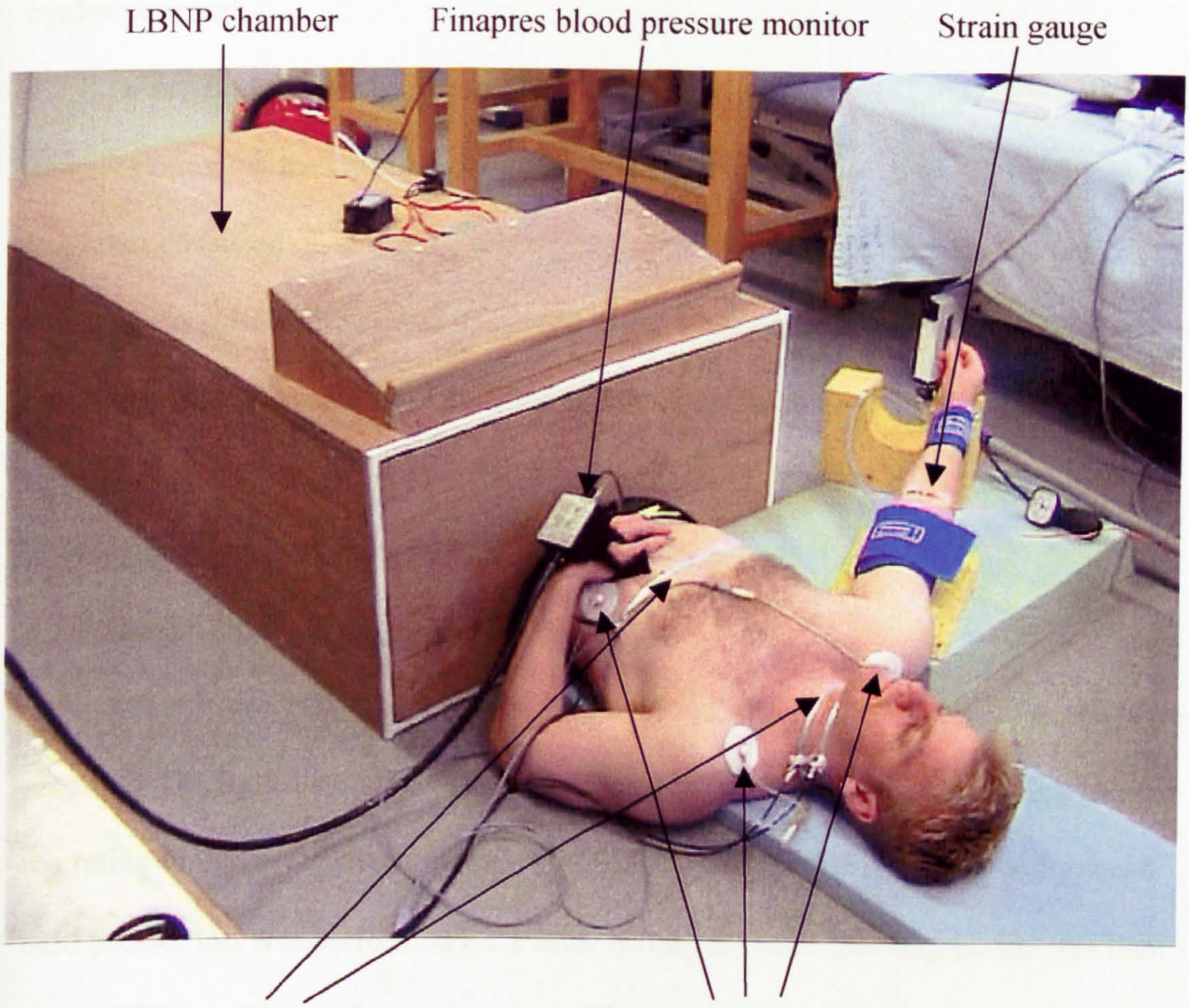


Figure 4.1. The experimental set-up.

4.1.1 Baseline

After a period of 10-min supine rest, blood pressure (BP) was measured manually, and the collection of cardiovascular data was initiated. Baseline measures were taken for 6 min, of which minutes four to six involved paced breathing (ten cycles per min).

4.1.2 Lower Body Negative Pressure

Following the baseline period a graded LBNP protocol, 0 to -20 mmHg, was used that consisted of -5 mmHg increments, 90 s at each stage. During this period forearm blood flow (FBF) was measured every 10 s over a 5 s sampling period, whilst cardiovascular measures and BP were recorded continuously. After the completion of the last stage, LBNP was adjusted in a graded fashion (1 mmHg/ 2 s) back to 0 mmHg, and subjects were given a 5-min recovery period.

4.1.3 Stress

The Stroop task was performed for a period of 2-min for which all errors were recorded. During a 1-min recovery period subjects were asked to rate the task using the rating of perceived exertion scale (Borg, 1962). After this recovery the forehead cold pressor test was performed for 1 min. A further 1-min recovery period was then given. FBF, cardiovascular measures, and BP were recorded continuously throughout.

4.1.4 Lower Body Negative Pressure and Stress

After a 5-min period of rest where no blood flow recordings were taken, the final stage was performed. This involved the subjects performing the stress protocol, as above, whilst a LBNP of -20 mmHg was applied during each task. One minute before the start of each task, LBNP was adjusted to -20 mmHg in a graded fashion (-1 mmHg/ 2 s). A 2-min recovery period was given between the Stroop and forehead cold pressor test (with no LBNP).

4.1.5 Maximal Oxygen Uptake

This was measured at the end of the protocol (see Chapter 3). See Appendix IG for a detailed protocol of Study I.

4.2 Statistical Analysis

A two factor mixed factorial analysis of variance (ANOVA) was conducted to identify main effects and interactions of the within and between subjects factors for cardiovascular variables. Analysis was conducted separately for each of the three protocols. For the LBNP protocol the within subjects factor consisted of five levels (baseline, and LBNP at -5, -10, -15, -20 mmHg) and the between subjects factor two levels (HIGH and MOD groups). For the stress and LBNP/stress protocols the within subjects factor also consisted of five levels (baseline, Stroop, recovery, cold pressor, recovery) and the between subjects factor two levels (HIGH and MOD groups).

The Mauchly sphericity test was performed to test for homogeneity of covariance in the within subjects factor. Non-homogeneity was corrected by employing the Greenhouse-Geisser test (Kinnear & Gray, 1999).

Following a significant simple main effect of the within subjects factor Bonferroni t-tests were then applied to make pairwise comparisons among the different levels. Significant main effects of the between subjects factor were tested by performing one-way ANOVAs on selected levels of the within subjects factors. Statistical significance was assumed at a value of $P<0.05$. All statistical procedures were performed using the *SPSS* computer software package.

4.3 Results

4.3.1 Subject Characteristics

Subject characteristics are displayed in Table 4.1. Eight subjects were assigned to the highly active group (HIGH) and 10 to the moderately active group (MOD). The

HIGH group was significantly older and displayed significantly higher levels of physical activity and $\dot{V}O_{2max}$ scores. The HIGH group also displayed significantly lower resting heart rate (RHR).

All subjects reported a history of hypertension that was apparent in first degree relatives. In the HIGH group all subjects reported a parental history of hypertension, seven of which reported a hypertensive father and one a hypertensive mother. In the MOD group six subjects reported parental history of hypertension, five of which reported a hypertensive father and one a hypertensive mother. The remainder of the MOD group reported family history of hypertension that was apparent in all subjects' grandmothers.

Table 4.1. Descriptive characteristics of moderately active (MOD; $n = 10$) and highly active (HIGH; $n = 8$) subjects with family history of hypertension (mean ± *SEM*).

Variable	MOD	HIGH
Age (years)	20.1 ± 0.6	25.5 ± 1.6 *
Body mass (kg)	74.3 ± 3.5	74.0 ± 3.5
Height (cm)	179.5 ± 2.3	179.5 ± 3.8
Body fat %	15.1 ± 1.0	13.1 ± 1.3
Physical activity ($kcal.kg^{-1}.d^{-1}$)	35.6 ± 0.7	42.3 ± 1.0 *
$\dot{V}O_{2max}$ ($ml.kg^{-1}.min^{-1}$)	46.2 ± 2.4	53.2 ± 3.0 *
State anxiety	30.1 ± 2.3	30.4 ± 2.6
RHR ($b.min^{-1}$)	60.7 ± 2	50.7 ± 4 *
SBP (mmHg)	116.9 ± 5.9	110.4 ± 9.3
DBP (mmHg)	60.9 ± 3.3	59.6 ± 5.6

* significant difference between groups.

4.3.2 Response to Lower Body Negative Pressure

During the graded LBNP protocol there was a significant main effect within subjects for forearm blood flow (FBF) [F (4, 64) = 16.19, P<0.05], forearm vascular resistance (FVR) [F (4, 64) = 10.87, P<0.05], stroke volume (SV) [F (4, 64) = 17.87, P<0.05], heart rate (HR) [F (4, 64) = 4.87, P<0.05], but not for mean arterial pressure (MAP). On closer inspection, FBF was significantly decreased and FVR increased during each stage of the graded LBNP protocol in comparison with baseline. SV was significantly decreased at all LBNP stages, except at -5 mmHg, compared with baseline. HR was significantly decreased at all LBNP stages, except at -20 mmHg, compared with baseline (see Table 4.2). There were no significant interaction or between subject effects. There were also no significant main effects within or between subjects for the cardiopulmonary slope (CPS). However, the MOD group seemed to display consistently greater CPS values compared with the HIGH during all LBNP stages except at -20 mmHg, although differences were not significant (see Figure 4.2 and Table 4.2). The lack of significant findings for the CPS may have due to the reduced n at some of the LBNP stages. This was because some individuals showed no change in SV at certain stages of the LBNP protocol thus making it impossible to calculate an individual's CPS for that specific LBNP stage.

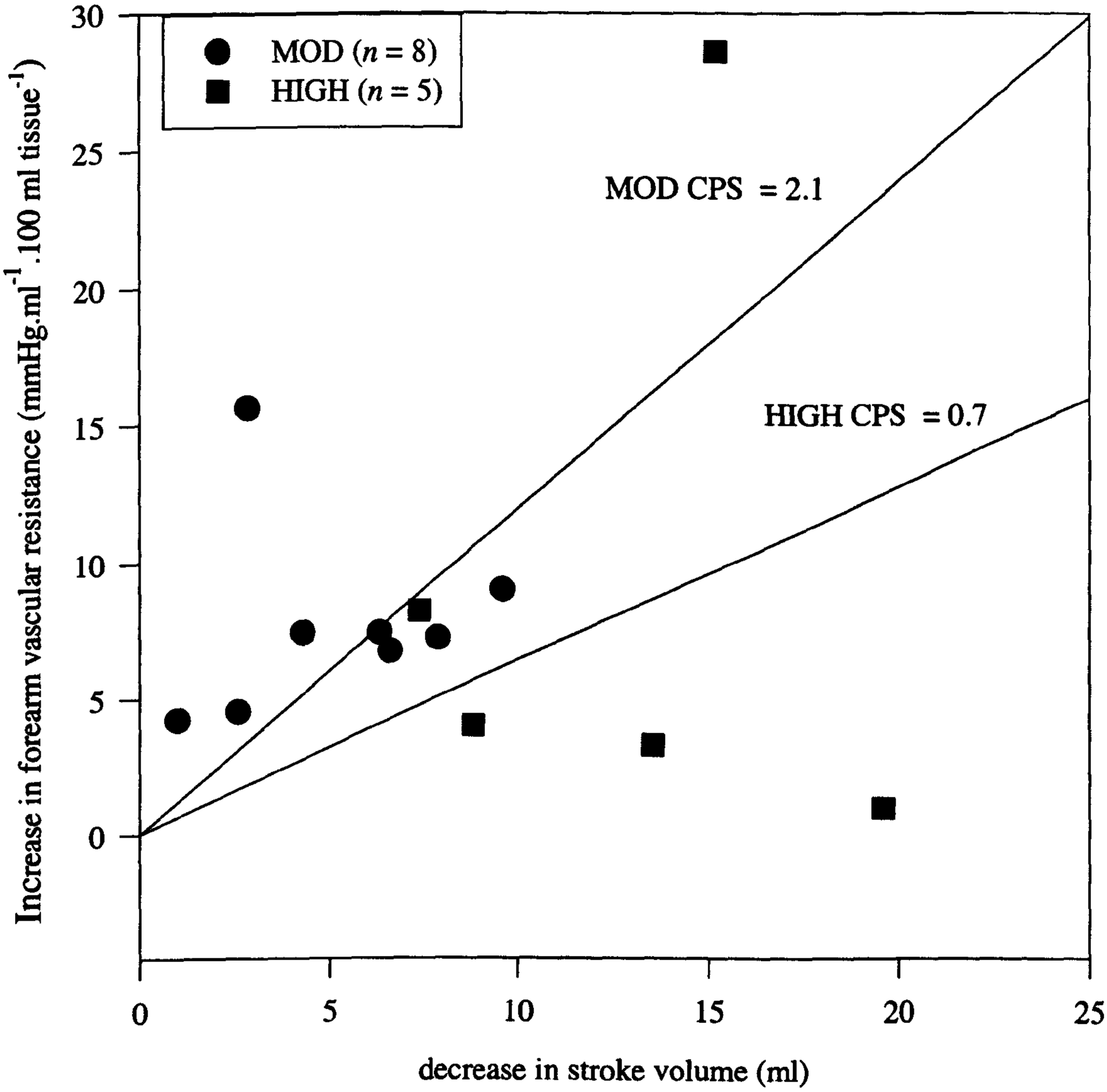


Figure 4.2. Response to lower body negative pressure at - 10 mmHg in moderately and highly active offspring hypertensives

Table 4.2. Response to lower body negative pressure in moderately active (MOD; n = 10) and highly active (HIGH; n = 8) individuals with family history of hypertension (mean ± *SEM*).

Variable	Condition									
	Baseline		-5 mmHg		-10 mmHg		-15 mmHg		- 20 mmHg	
	MOD	HIGH	MOD	HIGH	MOD	HIGH	MOD	HIGH	MOD	HIGH
HR (b.min^{-1})	60.7±2	50.7±4	57.1±3*	49.3±3*	56.5±2*	49.1±3*	57.6±2*	50.4±3*	58.7±3	49.3±3
SV (ml)	107.0±7	129.6±16	104.3±7	125.6±15	104.1±7*	122.4±14*	99.3±6*	118.9±14*	94.5±6*	118.6±14*
MAP (mmHg)	79.3±4	81.2±3	72.0±4	81.5±5	75.4±4	82.7±5	76.6±5	81.0±4	78.1±5	81.1±5
FBF (ml.100 ml tissue^{-1}.min^{-1})	3.1±.5	2.8±.4	2.3±.3*	2.1±.2*	2.4±.3*	2.2±.3*	2.3±.3*	2.2±.4*	2.2±.2*	1.9±.3*
FVR (mmHg.ml^{-1}.100 ml tissue^{-1})	26.2±2	34.0±5	36.7±6*	42.5±6*	34.3±3*	43.7±6*	38.1±6*	44.3±7*	39.1±4*	51.5±9*
CPS	-	-	2.2±1.3	1.6±.6	2.1±.6	0.7±.3	0.9±.3	0.6±.2	2.0±.6	2.1±.9

* significantly different from baseline.

4.3.3. Response to Stroop and Forehead Cold Pressor

During the Stroop mental challenge there was no significant differences in perceived task difficulty (mean ± *SEM*: 14.6 ± 0.6 versus 14.2 ± 0.5) or mistakes (15.2 ± 3.4 versus 15.0 ± 2.5) for the MOD and HIGH groups respectively.

4.3.3.1. Central cardiovascular responses. For HR there was a significant main effect [F (4, 64) = 52.14, P<0.05], interaction over time [F (4, 64) = 4.31, P<0.05], and between subjects effect [F (1, 16) = 11.65, P<0.05]. HR was significantly increased during Stroop, during recovery from Stroop, and significantly reduced during the cold pressor in comparison with baseline. Further analysis revealed that the MOD group displayed significantly greater increases in HR during Stroop compared with the HIGH group [F (1,16) = 17.28, P<0.05, ES = 0.86] and also that the HIGH displayed significantly greater recovery in HR after the Stroop [F (1,16) = 14.26, P<0.05, ES = 0.48] (see Figure 4.3a and Table 4.3). There were no group differences in response to the cold pressor or recovery from this task.

There was a significant main effect within subjects for cardiac output (CO) [F (4, 64) = 18.57, P<0.05], but no interaction or between subject effects. CO was significantly increased during Stroop and recovery from Stroop (see Figure 4.3b and Table 4.3).

There was a significant main effect within subjects for SV [F (4, 64) = 6.79, P<0.05], but no interaction or between subject effects. SV was significantly reduced during Stroop and significantly increased during the cold pressor (see Figure 4.3c and Table 4.3).

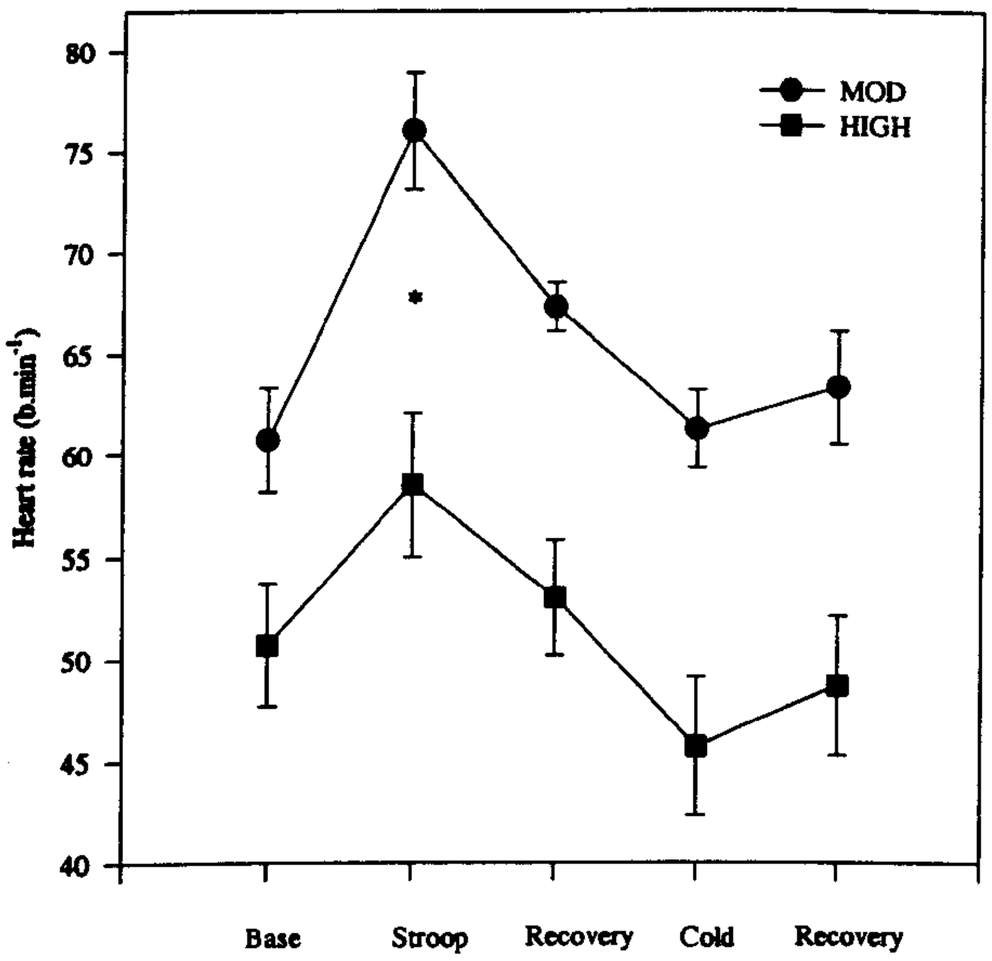


Figure 4.3a

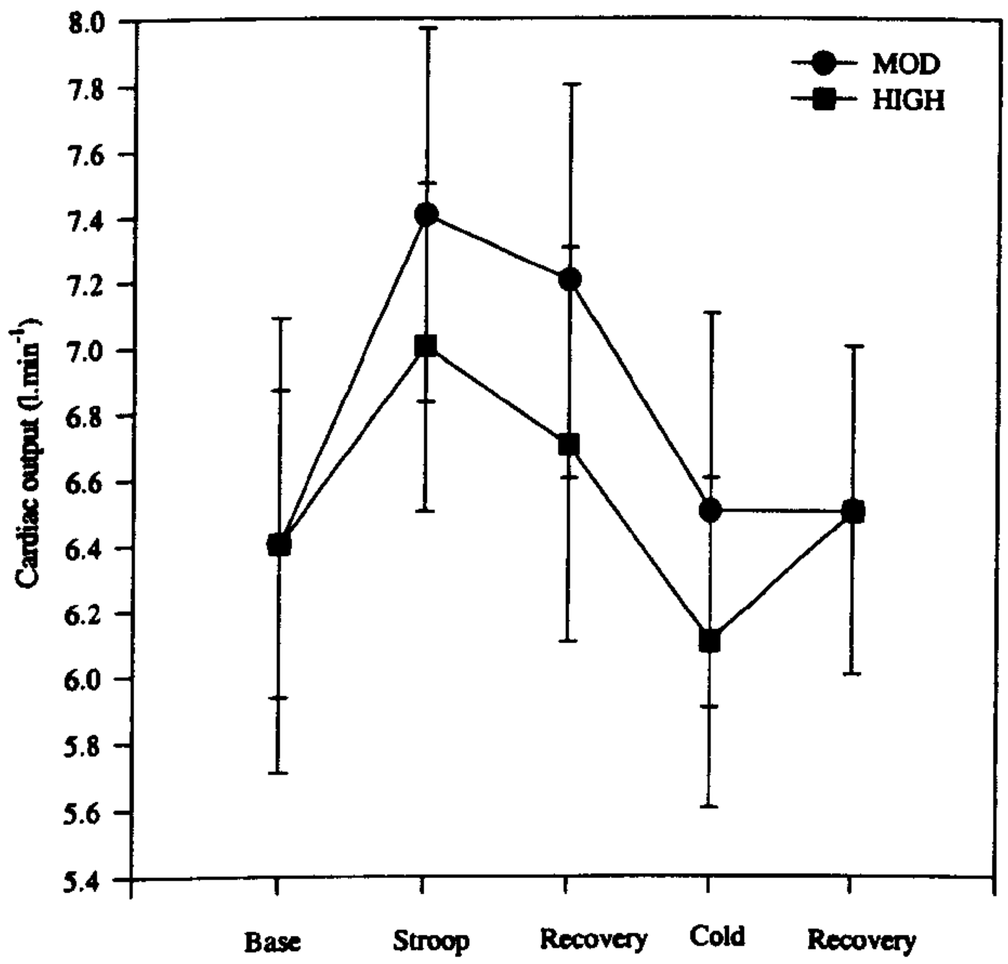


Figure 4.3b

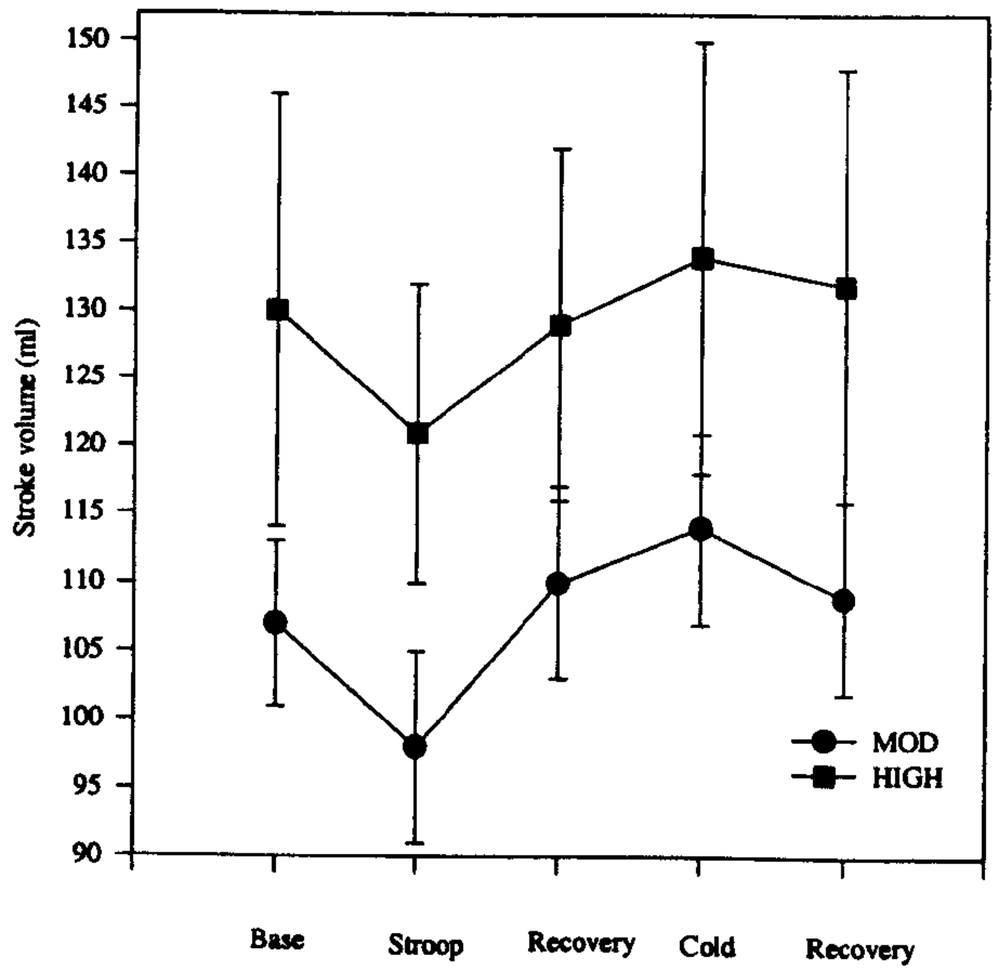


Figure 4.3c

Figures 4.3 a-c. Central cardiovascular responses to mental challenge and forehead cold pressor in highly active (HIGH) and moderately active (MOD) offspring hypertensives. * Significant difference in change score between groups.

4.3.3.2 Cardiac autonomic responses. There was a significant main effect within subjects for time series analysis of heart period variability (HPV_{ts}) in the high frequency domain (0.12-0.4 Hz) [F (4, 64) = 9.47, P<0.05], but no interaction or between subject effects. HPV_{ts} was significantly reduced during Stroop, recovery from Stroop, and during recovery from the cold pressor in comparison with baseline. However, HPV_{ts} was not significantly reduced during the cold pressor. There was no significant main effect or interaction within subjects and no between subjects effect for HPV_{ts} in the medium frequency domain (0.07-0.11 Hz). See Figures 4.4a and b and Table 4.3.

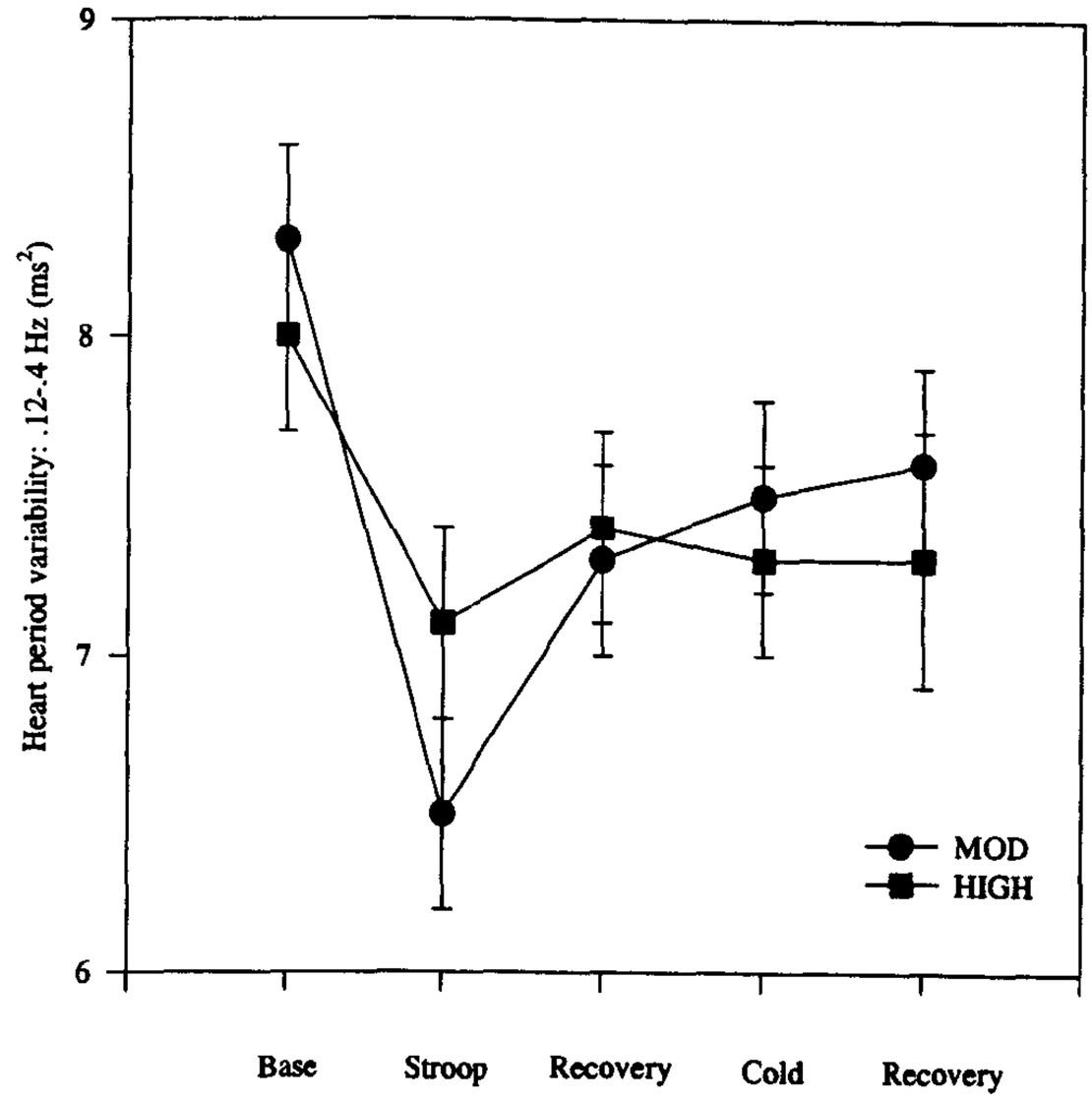


Figure 4.4a

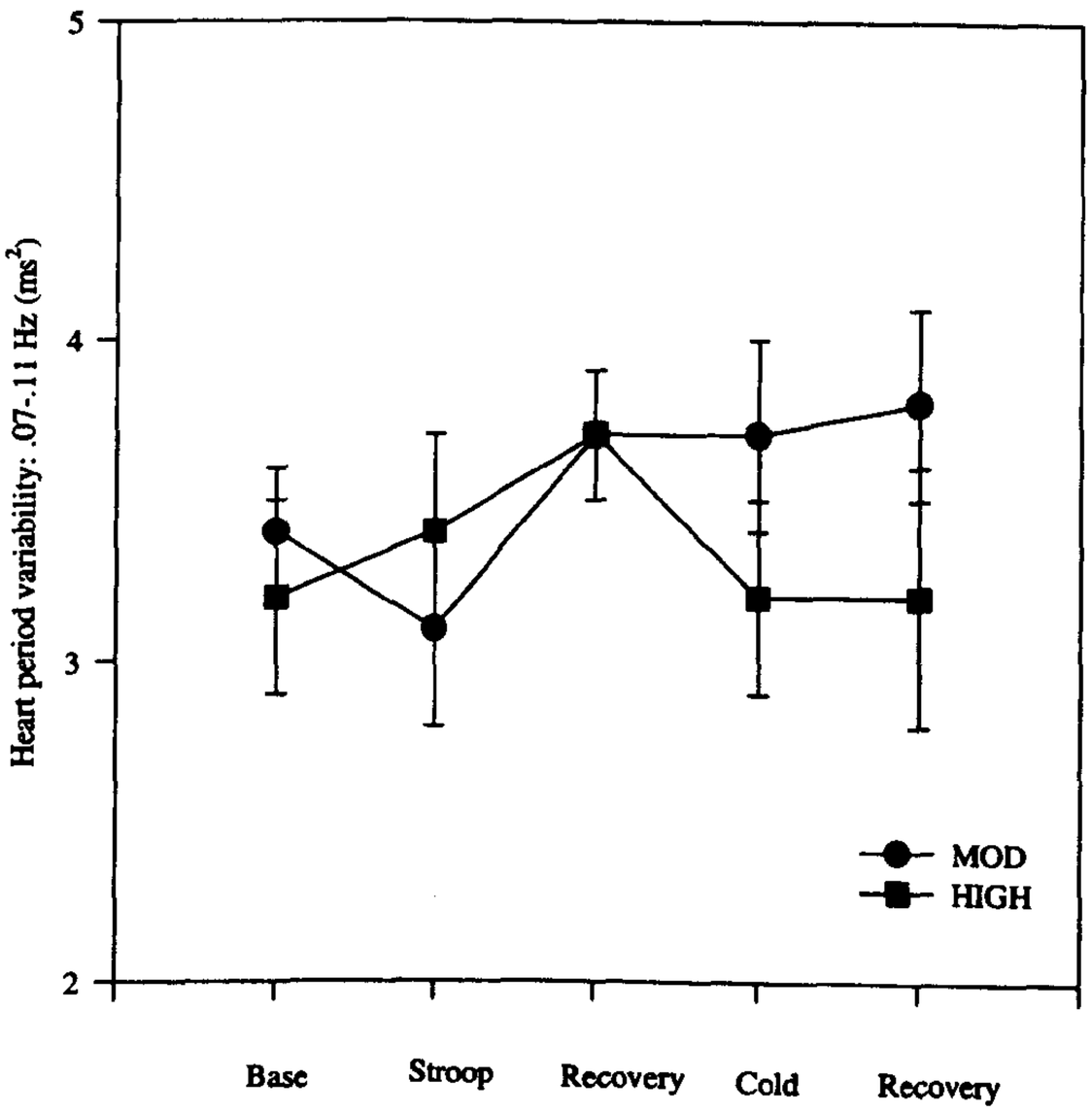


Figure 4.4b

Figures 4.4a and b. Cardiac autonomic responses to mental challenge and forehead cold pressor in highly active (HIGH) and moderately active (MOD) offspring hypertensives.

4.3.3.3 Cardiac contractility. There a significant main effect [F (4, 64) = 3.15, P<0.05], interaction over time [F (4, 64) = 2.59, P<0.05], and between subject effects [F (1, 16) = 4.55, P<0.05] for pre-ejection period (PEP). There was a trend for a decrease in PEP during the Stroop and PEP was significantly reduced during recovery from the Stroop in comparison with baseline. There were significant differences in PEP change during the Stroop and cold pressor between the groups. The MOD group demonstrated greater decreases in PEP during the Stroop in comparison with the HIGH. Also, during the cold pressor PEP was slightly reduced in the MOD but increased in the HIGH in comparison with baseline (see Figure 4.5a and Table 4.3).

There was a significant main effect over time for left ventricular ejection time (LVET) [F (4, 64) = 24.04, P<0.05], and between subject effects [F (1, 16) = 7.66, P<0.05], but no significant interaction over time. LVET was significantly reduced during the Stroop but increased during the cold pressor and recovery from this in comparison with baseline (see Figure 4.5b and Table 4.3).

There was a significant main effect for PEP/LVET (PL) ratio over time [F (4, 64) = 3.84, P<0.05]. PL ratio was significantly decreased during recovery from the cold pressor in comparison with baseline (see Figure 4.5c and Table 4.3).

There was no significant main effect although there was a significant interaction over time for Heather Index (HI) [F (4, 64) = 2.28, P<0.05]. The HIGH group displayed decreases in HI during the Stroop whereas the MOD group displayed increases in HI (see Figure 4.5d and Table 4.3).

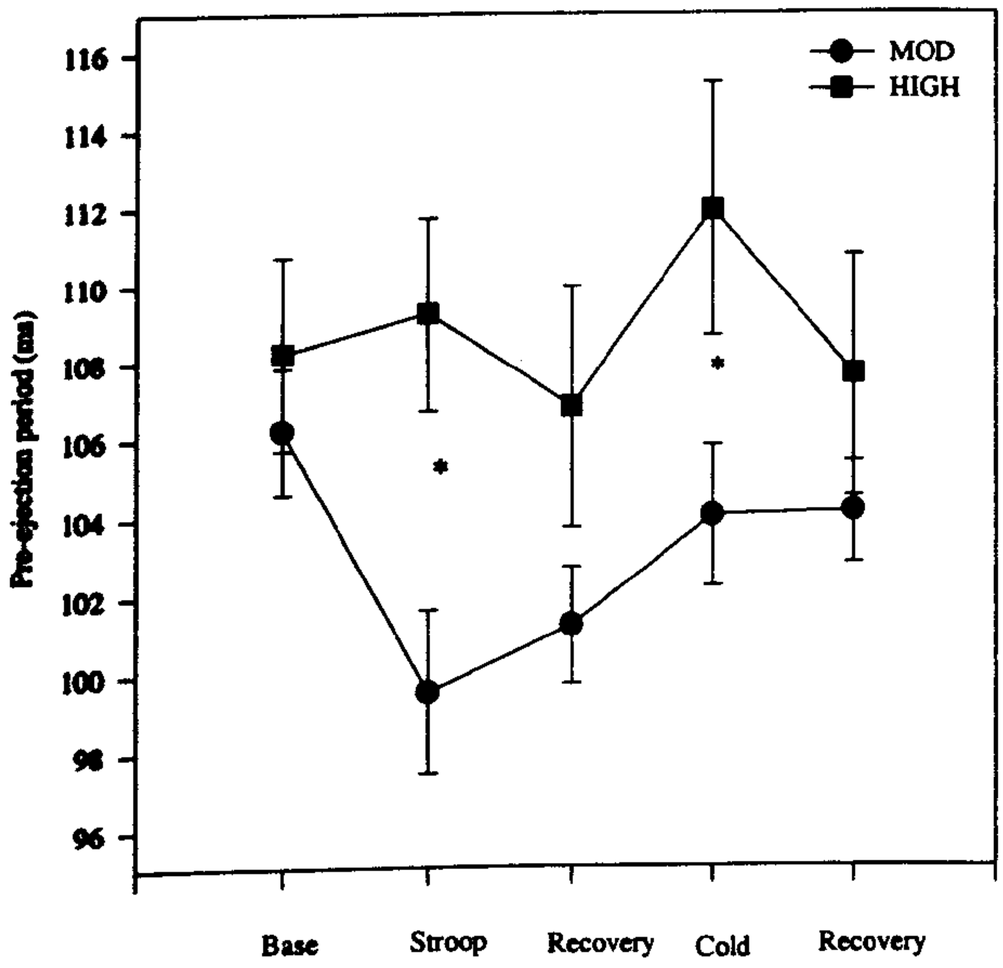


Figure 4.5a

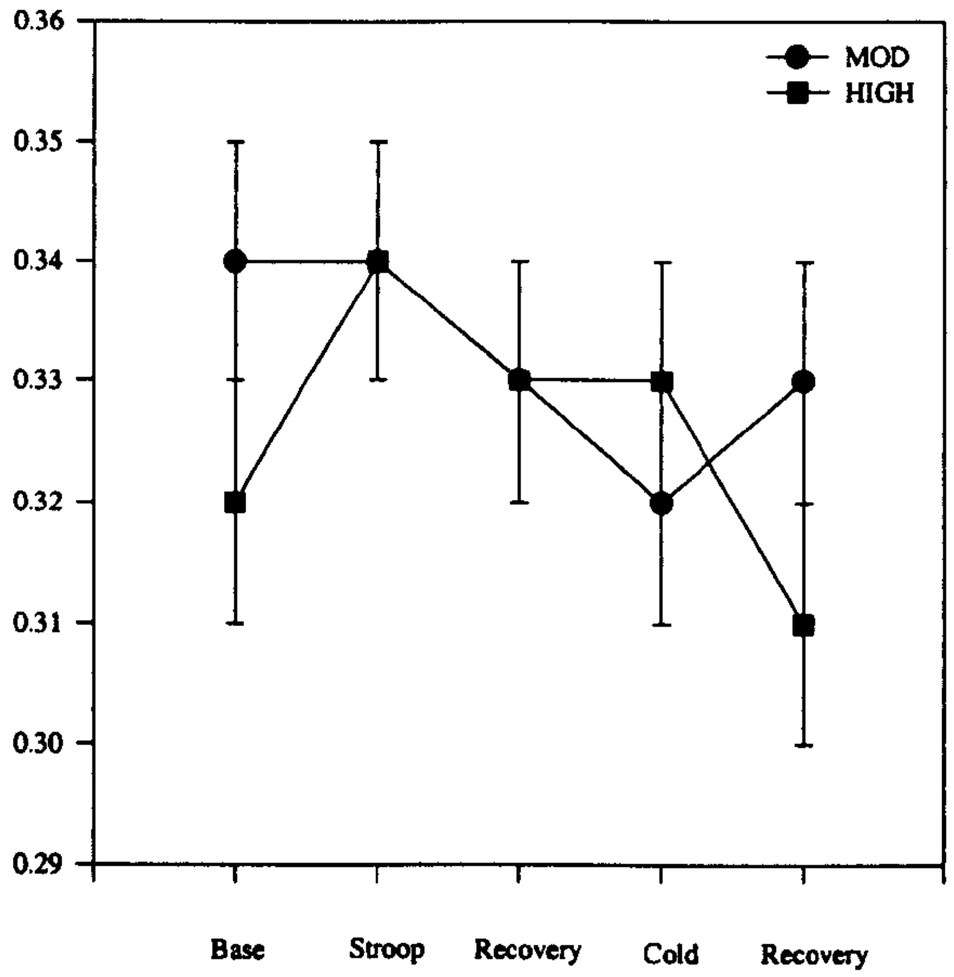


Figure 4.5c

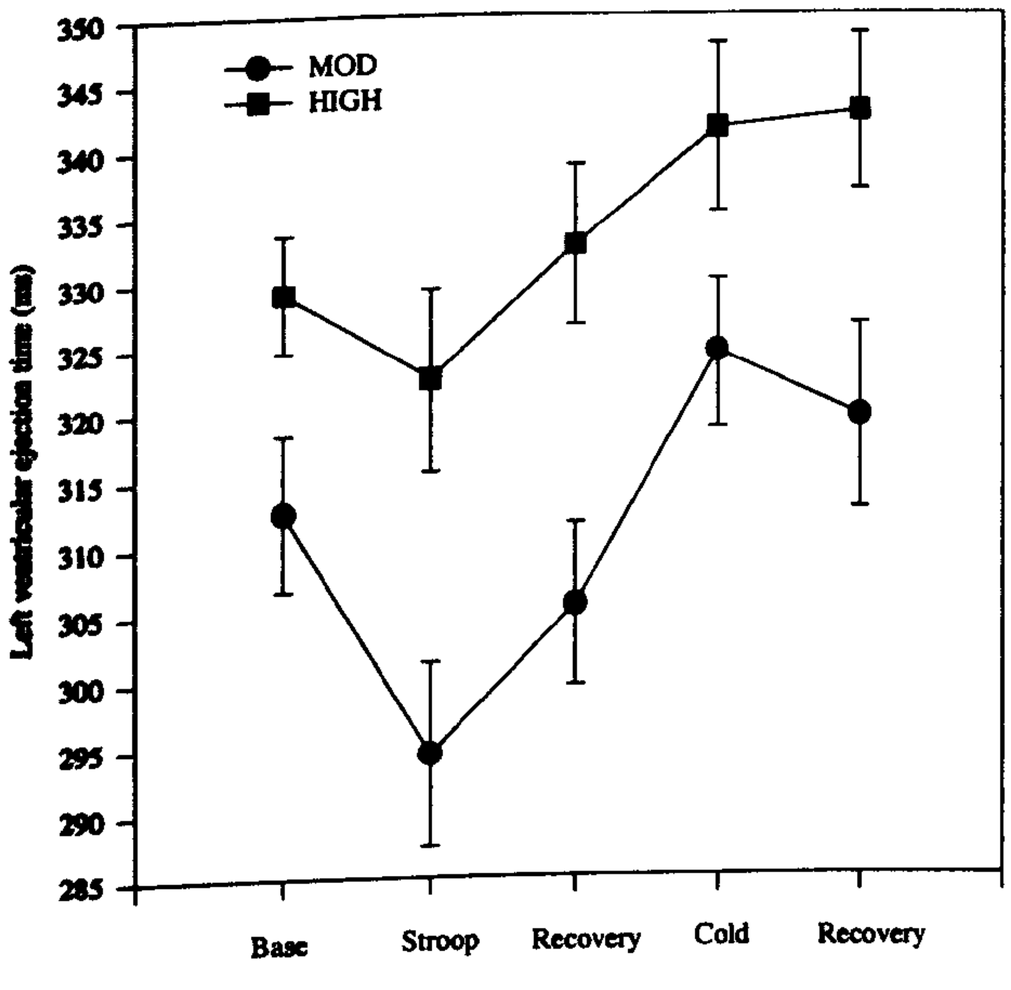


Figure 4.5b

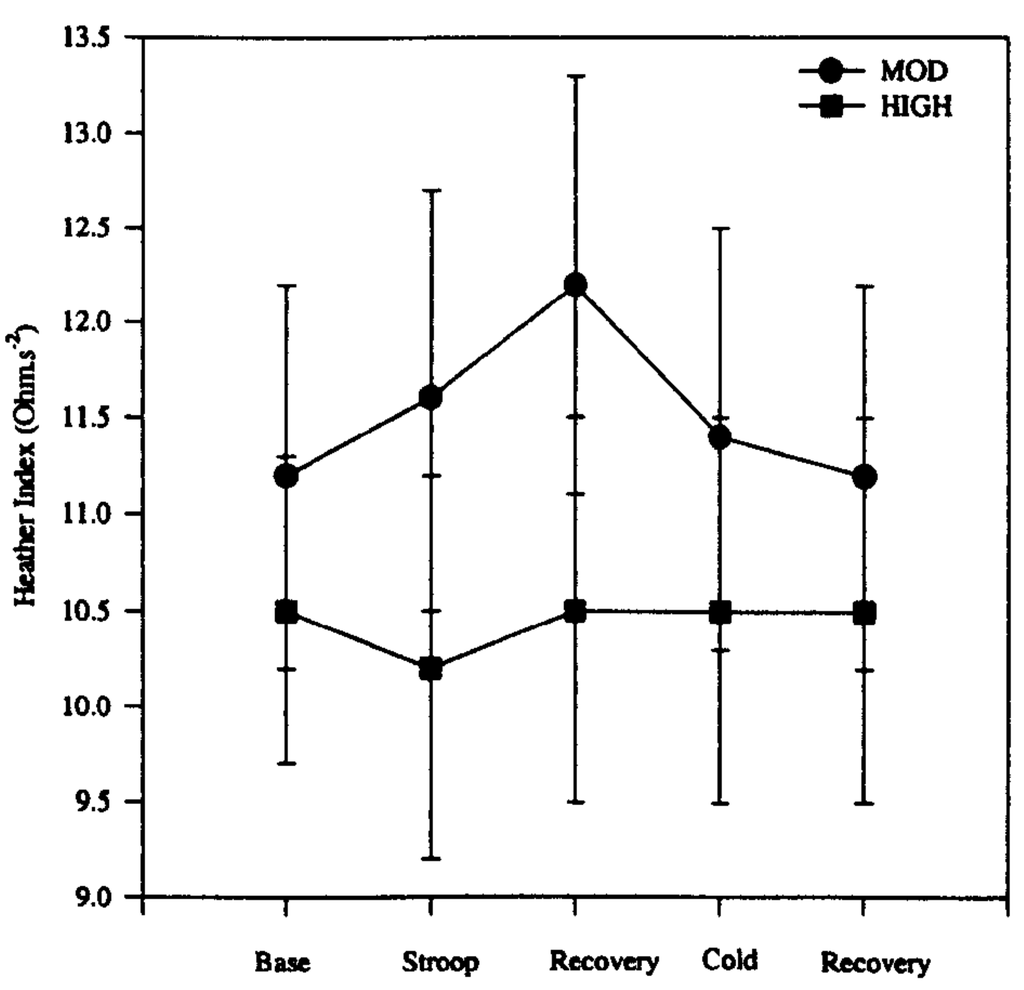


Figure 4.5d

Figures 4.5 a-d. Cardiac contractility responses to mental challenge and forehead cold pressor in highly active (HIGH) and moderately active (MOD) offspring hypertensives. * Significant difference in change between groups.

4.3.3.4 Blood pressure. There was a significant main effect within subjects for systolic blood pressure (SBP) [F (4, 64) = 3.76, P<0.05], diastolic blood pressure (DBP) [F (4, 64) = 5.13, P<0.05], and MAP [F (4, 64) = 13.75, P<0.05], but no interaction or between subject effects. SBP was elevated during Stroop and the cold pressor test but after applying Bonferonni adjustments, the elevations were not significant. However, both DBP and MAP were significantly elevated during Stroop, recovery from Stroop, cold pressor, and recovery from cold pressor (see Figures 4.6a-c and Table 4.3).

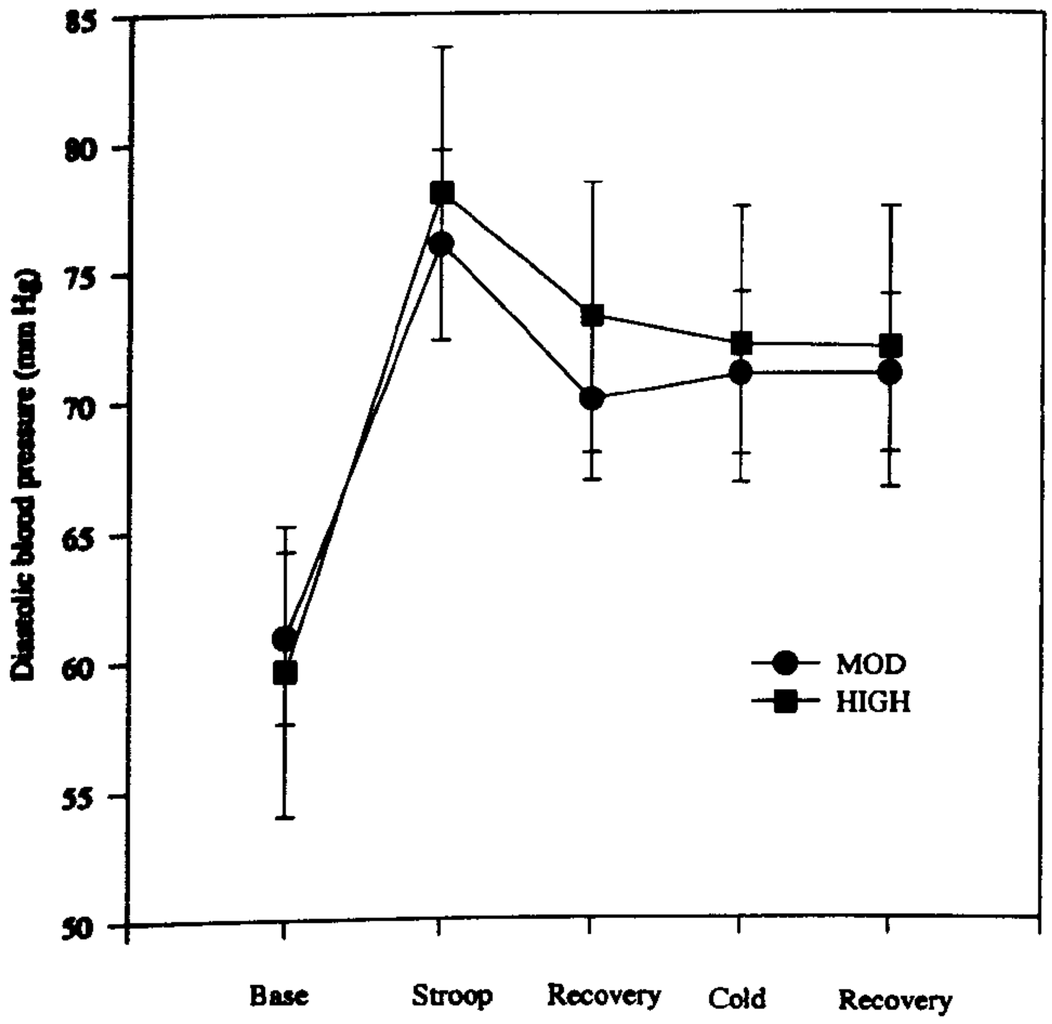


Figure 4.6a

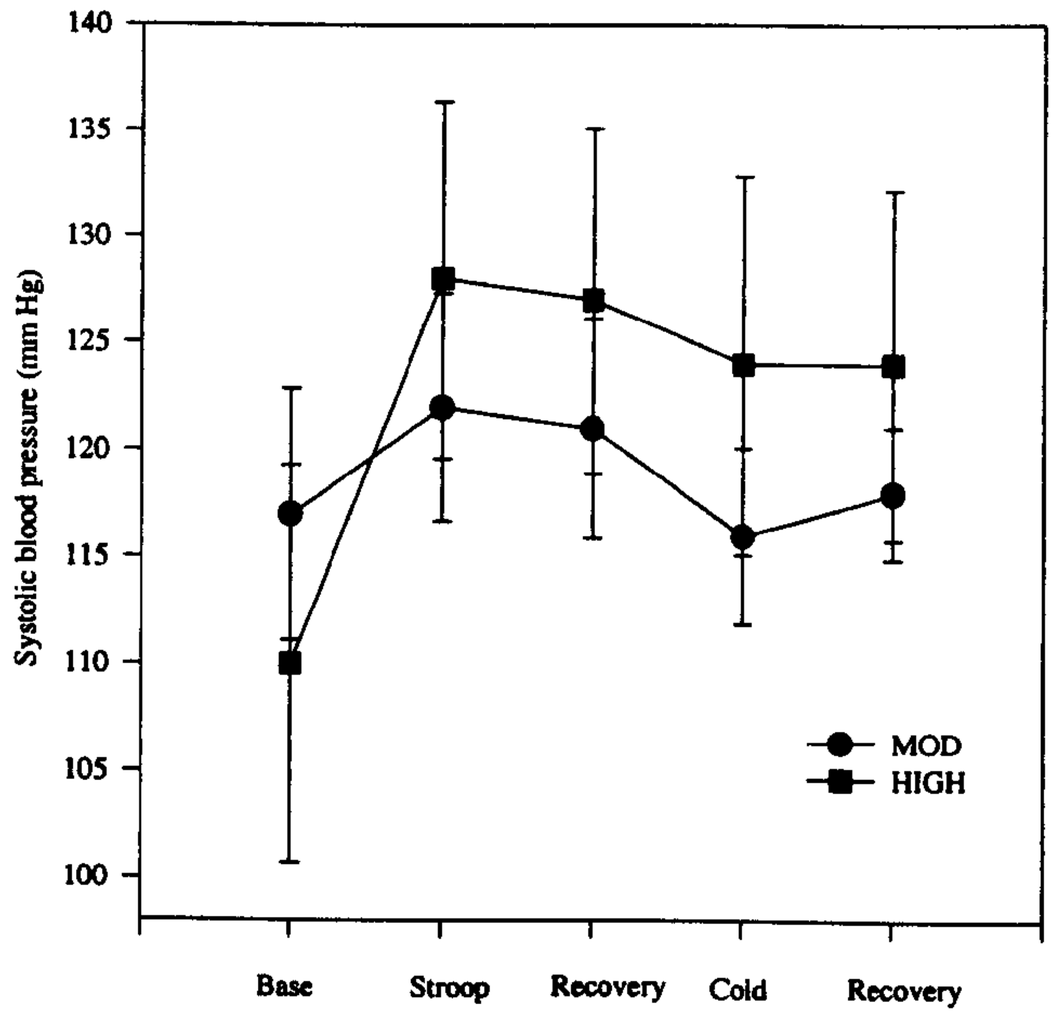


Figure 4.6c

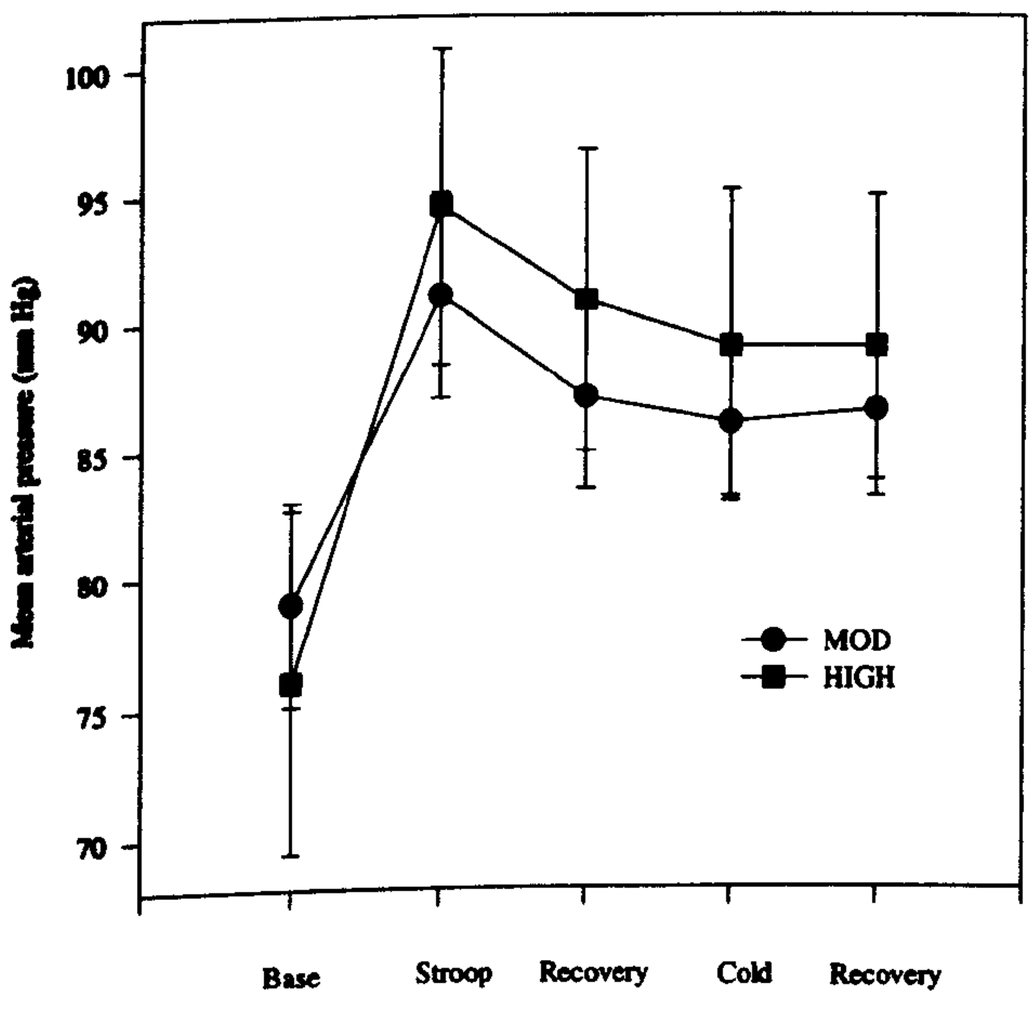


Figure 4.6b

Figures 4.6a-c. Blood pressure response to mental challenge and forehead cold pressor in highly active (HIGH) and moderately active (MOD) offspring hypertensives.

4.3.3.5 Peripheral vascular responses. There was a significant main effect within subjects for total peripheral resistance (TPR) [F (4, 64) = 6.17, P<0.05], but no interaction or between subject effects. TPR was significantly elevated during the cold pressor only (see Figure 4.7a and Table 4.3).

There was a significant main effect [F (4, 64) = 45.8, P<0.05], and interaction [F (4, 64) = 4.9, P<0.05] for within subject factors for FBF. FBF was significantly increased during Stroop and significantly reduced during the cold pressor in comparison with baseline. Subsequent analysis revealed that during Stroop the MOD group displayed a significantly greater increase in FBF compared with HIGH [F (1, 16) = 6.7, P<0.05, ES = 1.2] (see Figure 4.7b and Table 4.3).

There was a significant main effect within subjects for FVR [F (4, 64) = 21.43, P<0.05], but no interaction or between subject effects. FVR was significantly reduced during Stroop and significantly increased during the cold pressor in comparison with baseline (see Figure 4.7c and Table 4.3).

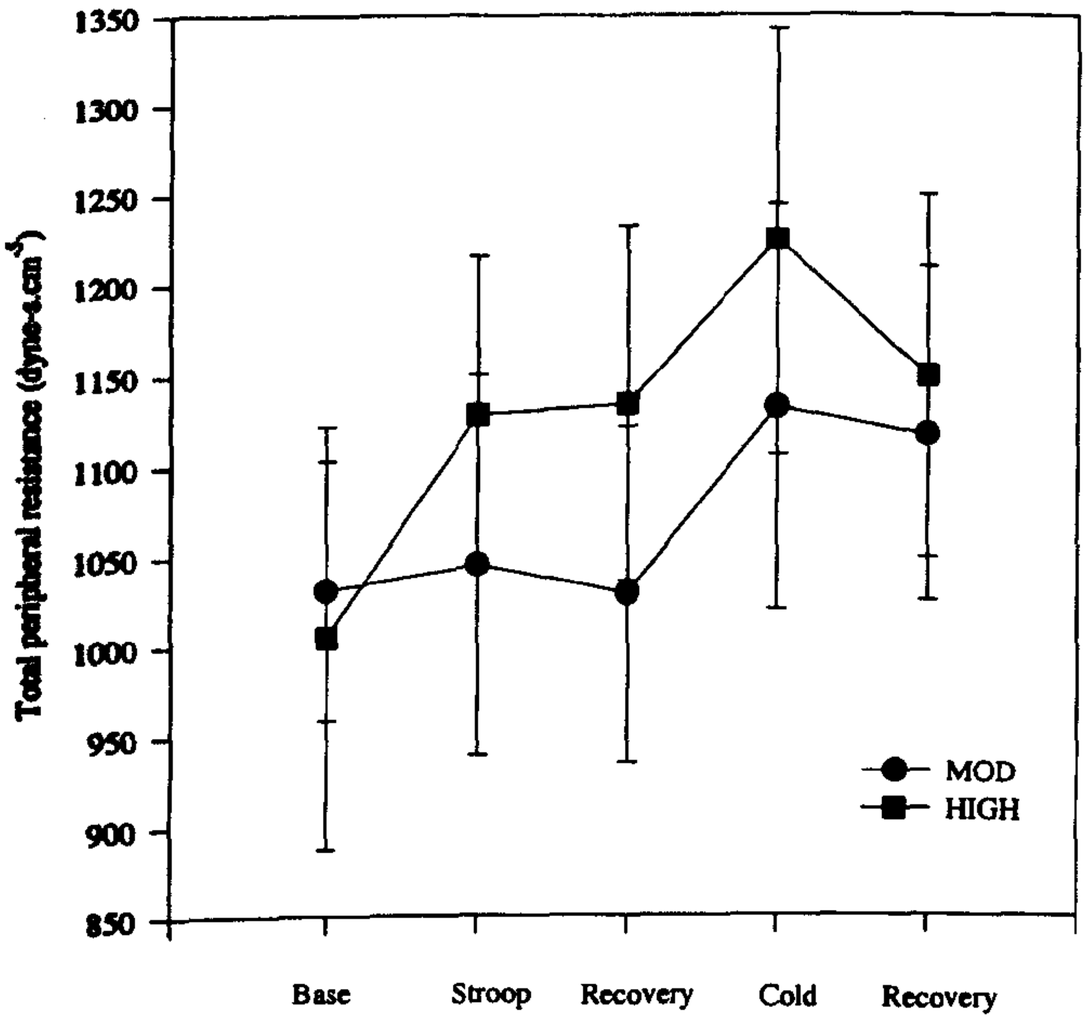


Figure 4.7a

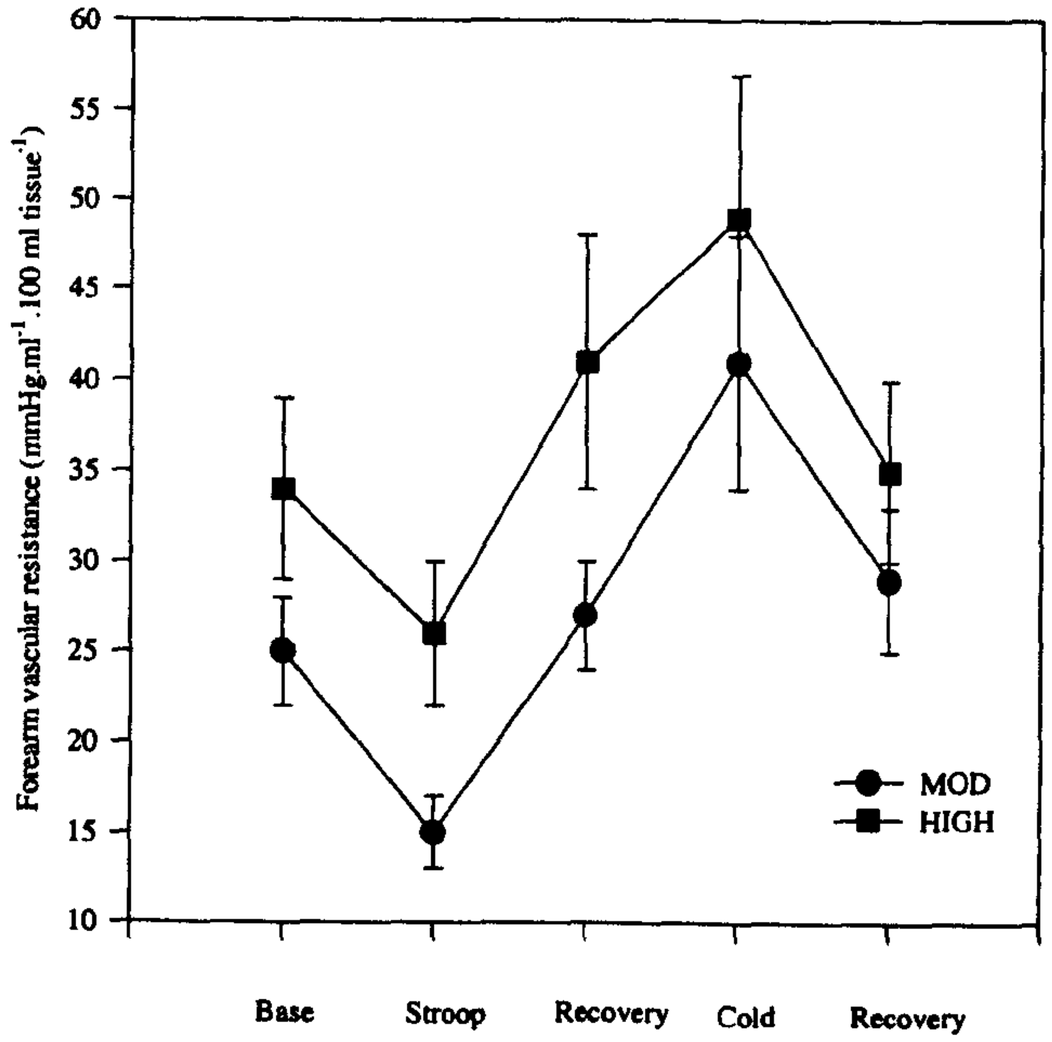


Figure 4.7c

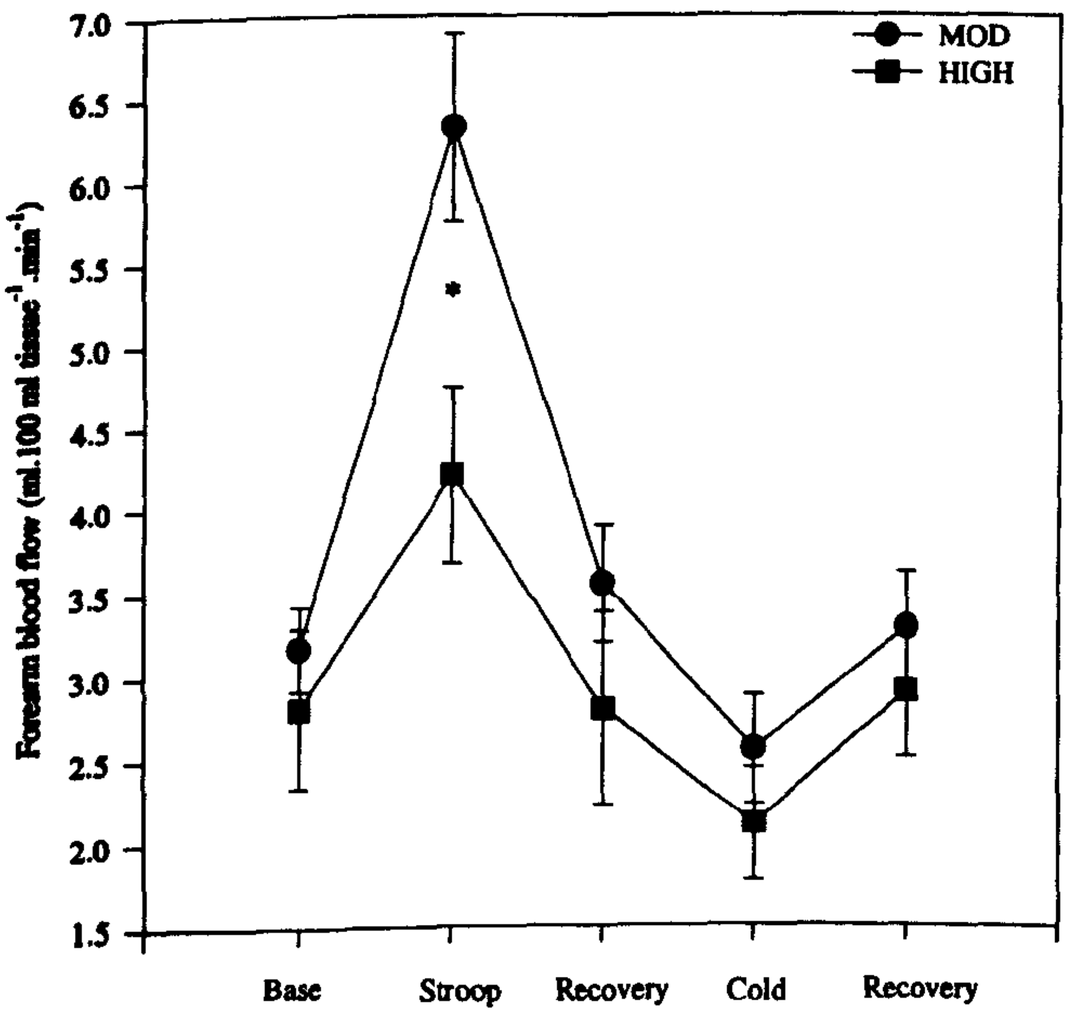


Figure 4.7b

Figures 4.7a-c. Peripheral vascular responses to mental challenge and forehead cold pressor in highly active (HIGH) and moderately active (MOD) offspring hypertensives. * Significant difference in change score between groups.

4.3.3.6 Overall patterning responses. Although the rise in blood pressure during Stroop was not significantly different between groups, each group demonstrated different cardiovascular patterning responses during Stroop; the MOD responded through elevated HR and CO (central responses), whereas the HIGH responded by elevated TPR (see Figures 4.3, 4.6, and 4.7).

Table 4.3. Response to mental challenge (Stroop) and forehead cold pressor test in moderately active (MOD; $n = 10$) and highly active (HIGH; $n = 8$) individuals with family history of hypertension (mean ± *SEM*).

Variable	Condition									
	Baseline		Stroop		Recovery		Cold pressor		Recovery	
	MOD	HIGH	MOD	HIGH	MOD	HIGH	MOD	HIGH	MOD	HIGH
HR ($b.min^{-1}$)	60.7±3	50.7±3	76.0±3	58.4±3*	65.0±2	52.0±2*	56.8±2	46.9±3	60.2±3	50.3±3
SV (ml)	106.9±6	129.6±16	98.2±7	120.9±11	110.0±7	129.2±13	114.3±7	133.8±16	108.8±7	132.4±16
CO ($l.min^{-1}$)	6.4±.5	6.4±.5	7.4±.6	7.0±.5	7.2±.6	6.7±.6	6.5±.6	6.1±.5	6.5±.5	6.5±.5
HPV_{ts} (.12-.4 Hz)	8.3±.3	8.0±.3	6.5±.3	7.1±.3	7.3±.3	7.4±.3	7.5±.3	7.3±.3	7.6±.3	7.3±.4
HPV_{ts} (.07-.11 Hz)	3.4±.2	3.2±.3	3.1±.3	3.4±.3	3.7±.2	3.7±.2	3.7±.3	3.2±.3	3.8±.3	3.2±.4
PEP (ms)	106.2±2	108.2±3	99.5±2	109.2±3*	101.2±2	106.8±3	104.0±2	111.9±3*	104.1±1	107.6±3
LVET (ms)	312.5±6	329.0±5	294.3±7	322.4±7	305.5±6	332.5±6	324.3±6	341.4±6	319.5±7	342.6±6
PL ratio	.34±.01	.32±.01	.34±.01	.34±.01	.33±.01	.33±.01	.32±.01	.33±.01	.33±.01	.31±.01
HI ($Ohm.s^{-2}$)	11.2±1	10.5±1	11.6±1	10.2±1	12.2±1	10.5±1	11.4±1	10.5±1	11.2±1	10.5±1
SBP (mmHg)	116.9±6	110.4±9	122.1±5	128.3±8	121.4±5	128.3±8	116.2±4	124.3±9	118.2±3	124.1±8
DBP (mmHg)	60.9±3	59.6±6	76.0±4	78.0±6	70.0±3	73.2±5	71.5±3	72.1±5	71.0±3	72.1±5
MAP (mmHg)	79.3±4	76.1±5	91.1±4	94.5±6	86.9±4	90.8±6	86.0±3	89.1±6	86.5±3	89.1±6
TPR ($dyne\text{-}s.cm^{-5}$)	1031±72	1005±117	1045±105	1128±87	1029±93	1134±98	1132±112	1224±118	1117±92	1149±99
FBF ($ml.100\ ml\ tissue^{-1}.min^{-1}$)	3.2±.2	2.8±.4	6.3±.6	4.2±.5*	3.5±.4	2.8±.5	2.5±.3	2.1±.3	3.3±.3	2.9±.4
FVR ($mmHg.ml^{-1}.100\ ml\ tissue^{-1}$)	25.0±3	34.3±5	15.3±2	26.5±4	27.7±3	41.3±7	41.1±7	49.6±8	29.0±4	35.9±5

* significant difference in change between groups in comparison with baseline.

4.3.4. Effects of Lower Body Negative Pressure During Response to Stroop and Cold Pressor

The rationale for the final part of the protocol was to examine cardiopulmonary (C-P) baroreceptor function during stress. Comparisons were made between FBF responses to Stroop and cold pressor with and without LBNP for each group (MOD and HIGH) separately. It can be seen from Figures 4.8a and b that in both groups LBNP attenuated but did not abolish the forearm vasodilatation response to Stroop. In MOD and HIGH groups FBF was increased by 71.5 ± 10.6% and 38.9 ± 14.0% respectively during Stroop only and 36.1 ± 20.6% and 24.2 ± 20.6% during Stroop plus LBNP. In the MOD group there was a significant interaction over time between the two conditions for FBF [F (4, 72) = 6.19, P<0.05]. Further analysis revealed that FBF was significantly reduced during LBNP and Stroop compared with Stroop alone [F (1, 18) = 11.51, P<0.01]. There were no significant interaction effects over time in the HIGH group suggesting that the LBNP did not have as pronounced an effect compared with the MOD group. There was no significant interaction or main effects for the cold pressor for either group suggesting that the involvement of the cardiopulmonary baroreceptors was specific to the mental challenge.

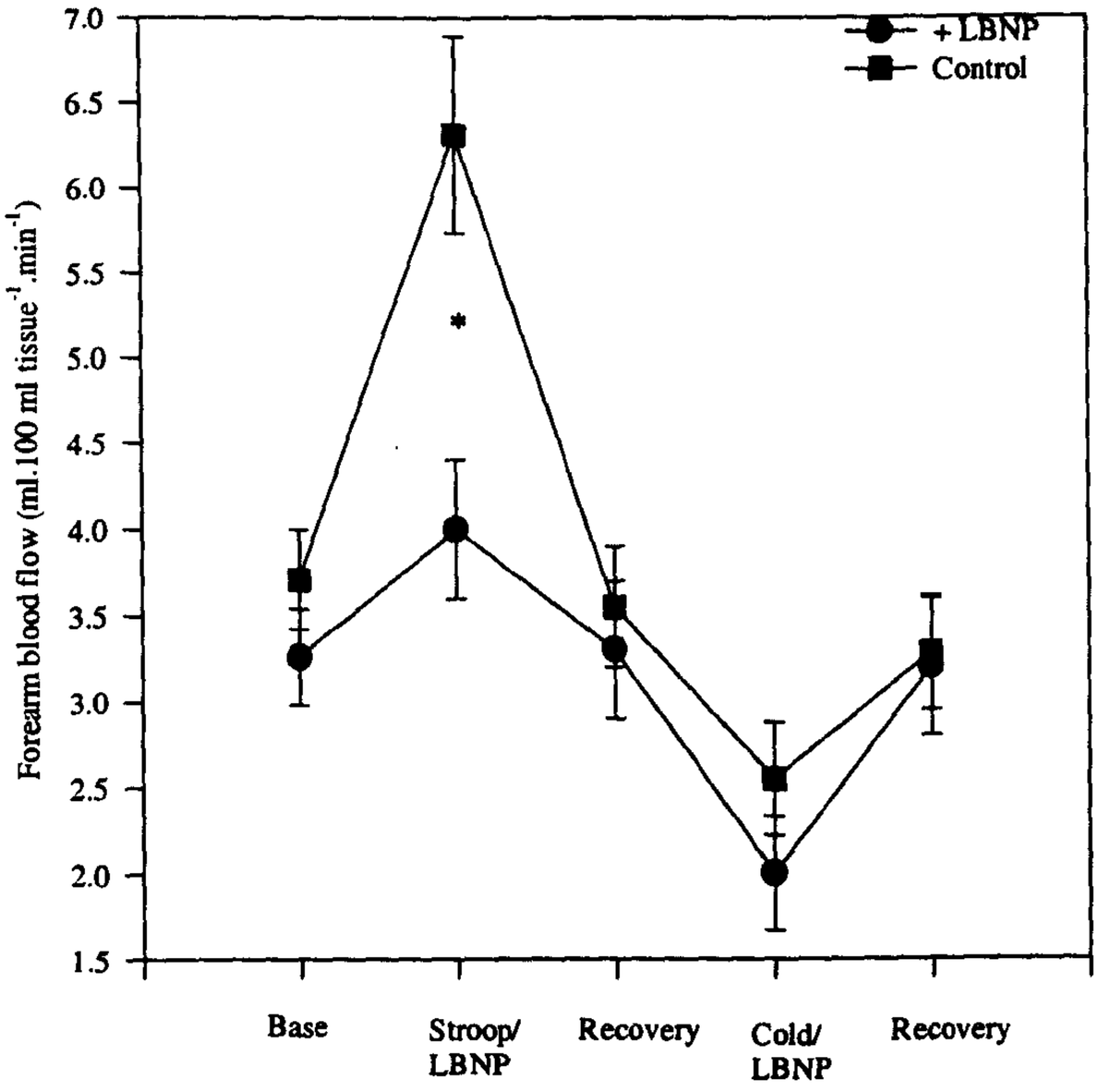


Figure 4.8a. The effect of lower body negative pressure on forearm blood flow response to Stroop and cold pressor in moderately active offspring hypertensives.
* Significant difference between conditions.

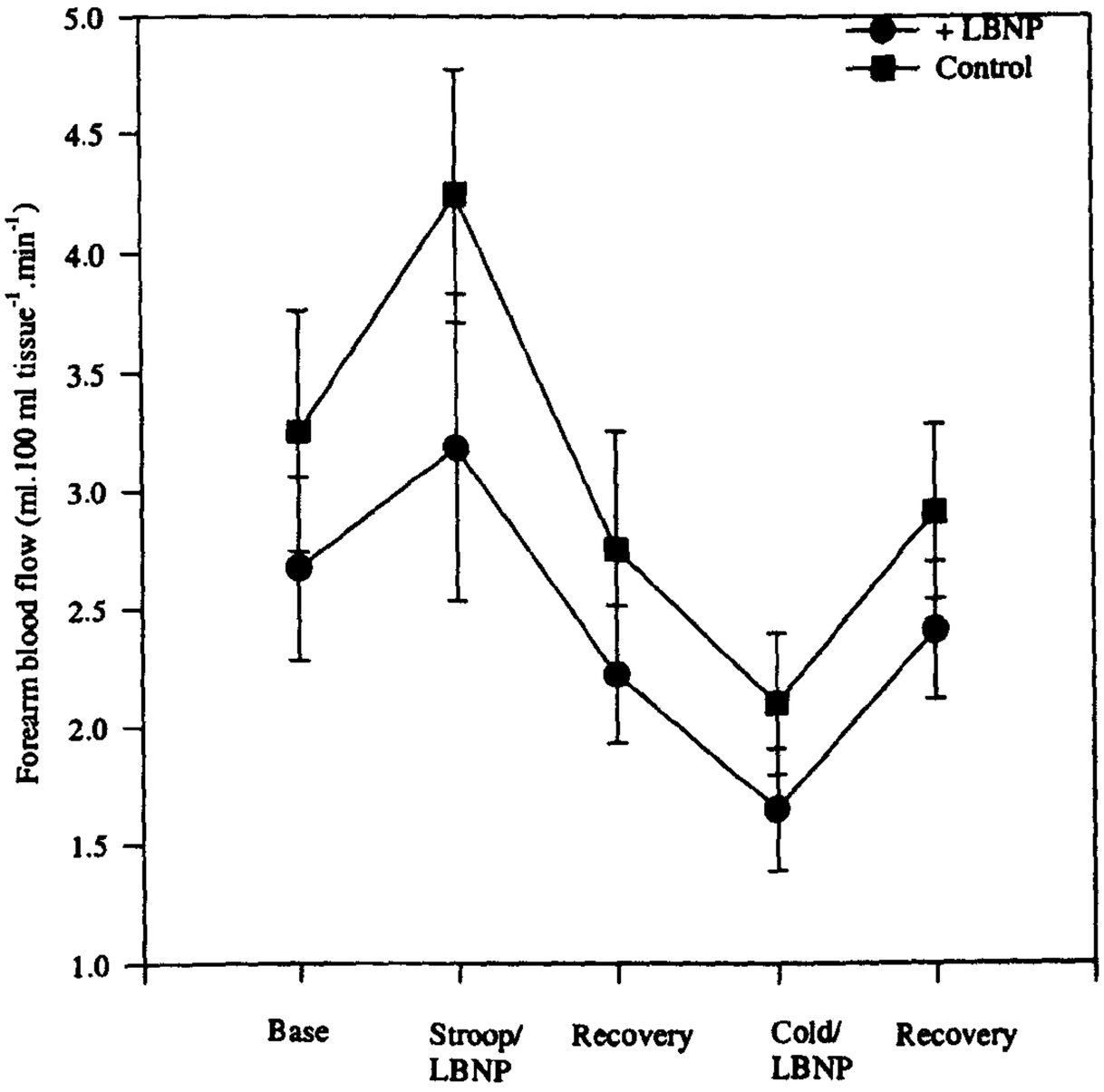


Figure 4.8b. The effect of lower body negative pressure on forearm blood flow response to Stroop and cold pressor in highly active offspring hypertensives.

4.4 Discussion

The purpose of the present study was to assess cardiovascular functioning in moderately and highly active offspring hypertensives during a number of tasks designed to activate the SNS. As predicted, the less active offspring hypertensives demonstrated an exaggerated HR and vascular response to mental challenge in comparison with the highly active. These differences in cardiovascular reactivity existed despite all subjects perceiving the task to have a similar level of difficulty and also being normotensive, healthy, and aerobically fit individuals. The results confirm previous findings by Holmes and Cappo (1987) who also showed an exaggerated HR response to mental challenge in less fit offspring hypertensives in comparison with their highly fit counterparts and controls. However, to the knowledge of the present investigator there is no research to date that has shown a reduced FBF reactivity to mental challenge in highly active compared with less active offspring hypertensives. Although a control group of subjects without family history of hypertension was not employed in the present study, the absolute FBF response demonstrated by the HIGH group was comparable to responses demonstrated by subjects without family history of hypertension in other studies during mental challenge (Anderson *et al.*, 1987; Halliwill *et al.*, 1997). This, therefore, suggests that the FBF response to stress demonstrated by the MOD was an exaggerated response compared to that of the HIGH, which was normal.

4.4.1 Hyper-reactive Stress Response

The sympathetic nervous system has been implicated in the hyper-reactive response to stress in offspring hypertensives. Familial differences in HR response to an active coping stressor have been reported to be abolished following β-adrenergic blockade (Miller & Ditto, 1991). Further research by Miller (1994) has indicated that

the parasympathetic nervous system (vagal withdrawal) plays little role in the exaggerated HR response and that it is primarily mediated by the SNS. This is in agreement with the present findings because the greater HR response in the moderately active group was accompanied by significantly greater decreases in PEP. Because loading conditions on the heart and the level of vagal withdrawal during mental challenge was not different between the two groups this, therefore, suggests a greater level of cardiac sympathetic activation in the moderately active. Miller and Ditto (1991) have also shown by selective pharmacological blockade that the forearm vasodilatation response to stress is reinforced by β-2 adrenergic or cholinergic activity.

4.4.2 Vascular Remodelling

The impact of repeated episodes of vascular hyper-reactivity may contribute to the development of hypertension. An over perfusion in certain vascular beds may be responsible for a remodelling process involving hypertrophy of vascular smooth muscle that would eventually cause permanent increases in vascular resistance (Folkow, 1990). Recently, Macnair (2000) described the link between a vascular remodelling process and low levels of physical activity. It was suggested that over perfusion of inactive muscle, with a low requirement for oxygen, would produce a chain of events resulting in the production of angiotensin II, which is one of the strongest vasoconstricting hormones in the human body. This would lead to a vascular remodelling process with the vasomotor system becoming hypersensitive to vasoconstrictor stimuli resulting in the resistance change described by Folkow (1990).

4.4.3 Renal Hemodynamics

A further explanation for the exaggerated forearm vasodilatation response to stress may be differences in regional blood flow because CO and BP were not

significantly different between the groups. The findings by Hollenburg *et al.* (1981) who showed a reduced kidney blood flow during mental stress in offspring hypertensives suggest that those individuals demonstrating a large forearm vasodilator response to stress may experience a large vasoconstrictor response in other vascular beds such as the kidney. Activation of the renal α-adrenergic receptors is thought to induce sodium retention through activation of the renin-angiotensin-aldosterone system (RAS) causing renal constriction (DiBona, 1982). Thus, the interaction of a kidney vasoconstrictor response with the RAS may be an important early contributor to the development of hypertension. This is because the RAS is integrally involved with sodium and fluid balance in the body and the retention of sodium is thought to play a role in both the development and maintenance of hypertension. Light, Koepke, Obrist, and Willis (1983) showed that in offspring hypertensive men, the degree of retention was directly related to the magnitude of HR increase during stress suggesting common mediation by way of the SNS.

4.4.4 Stress Reactivity Lowering Mechanisms of Physical Activity

That the highly active offspring hypertensives demonstrated a reduced cardiac and vascular reactivity to mental challenge suggests habitual physical activity may be associated with a reduced cardiovascular reactivity to mental challenge. The mechanism is most likely linked with the SNS. Possible explanations include altered sympatho-adrenal activation (releasing reduced amounts of epinephrine into the blood) or sensitivity of the β-adrenergic receptors.

A number of longitudinal training studies have observed a significant reduction in plasma catecholamine level after the training period (Duncan *et al.*, 1985; Jennings *et al.*, 1986). However, because plasma catecholamine levels represent a measure of average sympathetic neural activity it is difficult to determine whether

central, peripheral, or local mechanisms are primarily or secondarily responsible for the changes. Baroreceptor functioning has also been implicated as a mechanism in reducing sympathetic activity through exercise training.

4.4.5 Cardiopulmonary Baroreceptor Activity at Rest and During Stress

There were no significant differences in C-P baroreceptor function at rest between the two groups in the present study despite the trend for lower cardiopulmonary slopes in the highly active. This was unexpected as Mack *et al.* (1987; 1991) have shown that C-P baroreceptor function is depressed in trained compared to untrained individuals and this effect was also apparent after a longitudinal training study. Also Ueda *et al.* (1989) have shown that C-P baroreceptor function is augmented in offspring hypertensives.

However, there was evidence to suggest different C-P baroreceptor functioning during mental stress between the MOD and HIGH. The forearm vasodilatation response to mental stress in humans is thought to be mediated by sympathetic withdrawal and β-adrenergic mechanisms (Halliwill *et al.*, 1997). The present findings suggest that during mental stress the C-P baroreceptors are excited because when these receptors are inhibited, by LBNP, the vasodilatation response to stress is attenuated, but responses to the cold pressor are unaffected. Thus, sympathetic withdrawal during stress-induced vasodilatation may be due to excitation of C-P baroreceptors producing an increased inhibition of sympathetic neural outflow. That the MOD demonstrated a greater attenuation in FBF response to the Stroop during LBNP compared with the HIGH suggests they may have greater C-P baroreceptor excitation and hence more sympathetic withdrawal during stress. Mark and Kerber (1982) have suggested that an augmented inhibitory influence of C-P baroreceptors is related to impairment of arterial baroreceptor function. A number of

authors have found a damping of the arterial baroreceptor reflex during mental stress (Ditto & France, 1990; Sleight, 1978; Steptoe & Sawada, 1989). Thus, during stress an augmented C-P baroreceptor activity may be related to diminished arterial baroreceptor sensitivity. Buckworth *et al.* (1994) found that the carotid-cardiac baroreflex was attenuated during mental arithmetic compared with rest in moderately active offspring hypertensive women but not in the highly active group. Thus, these findings support the present results, which demonstrate augmented C-P baroreceptor function during stress in the moderately active offspring hypertensives. Ditto and France (1990) have also shown that diminished arterial baroreceptor sensitivity during stress may be a characteristic of offspring hypertensives. Given that strong correlations between baroreflex sensitivity and daily BP variability have been found (Sleight, 1983), these mechanisms may be related to the enhanced stress reactivity displayed by offspring hypertensives. Therefore, baroreceptor dysfunction in offspring hypertensives may be more important during stress.

4.4.6 Cardiovascular Recovery from Stress

A recent meta-analytic review to evaluate the effect of various hypertension risk factors on cardiovascular recovery from stress identified that high-risk individuals exhibited delayed cardiovascular recovery in comparison with low-risk individuals (Schuler & O'Brien, 1997). In particular, delayed HR recovery was associated with lack of physical fitness. This is in agreement with the present findings because the moderately active offspring hypertensives displayed significantly delayed HR recovery following mental challenge in comparison with the highly active offspring hypertensives. Gerin and Pickering (1995) have also shown that offspring hypertensives have significantly elevated SBP following recovery from mental challenge, in comparison with controls. However, this trend was not apparent in the

present study comparing BP recovery from mental challenge in moderately and highly active offspring hypertensives. Cardiovascular recovery from stress may be another important aspect of reducing hypertension risk because individuals who can recover more quickly from the stressor will have lower exposure to the damaging effects of the SNS on the cardiovascular system. Thus, physical activity level may be associated with greater cardiovascular recovery from stress.

4.4.7 Pressor Responses

No significant differences between the groups in response to the cold pressor test were observed. This is in agreement with the majority of previous research (see Muldoon review). Thus, these findings suggest cardiovascular responses to the cold pressor test are not strong risk markers in offspring hypertensives. However, two studies (Menkes, Matthews, & Krantz, 1989; Wood, Sheps, Elveback, & Schirger, 1984) have shown that large pressor responses to the cold pressor test predict development of hypertension over follow-up intervals of 47 and 20-36 years. This relationship persisted after adjustment for age, resting BP, body mass, cigarette smoking, and family history of hypertension.

In contrast to the pressor responses elicited by the cold pressor test, some studies have indicated exaggerated vascular or pressor responses, or lower threshold response to infused norepinephrine in offspring hypertensives (Bianchetti *et al.*, 1984; De Lima *et al.*, 1990; Doyle & Fracerm, 1961). Other researchers have demonstrated an exaggerated sympathetic neural outflow in offspring hypertensives (Yamada *et al.*, 1988).

4.4.8 Cardiovascular Pattering Responses

A further difference between the groups was their different cardiovascular patterning response during mental challenge. Julius (1993) has described a

hyperkinetic circulation that is thought to represent an early phase in the development of hypertension. This is characterised by higher HR and CO, which was the pattern of response demonstrated by the moderately active group during mental challenge. In comparison, the rise in BP in the highly active group was mainly characterised by an increase in TPR. This hyperkinetic response may be a strong predictor for the future development of hypertension because it has been previously observed in offspring hypertensives during exercise (Nho, Tanake, Kim, Watanabe, & Hiyama, 1998; van den Bree, Schieken, Moskowitz, & Eaves, 1996). The SNS is again thought to play a key role in the hyperkinetic circulation response.

4.4.9 Summary

In summary, this study provides evidence for an association between high levels of physical activity and a lower stress reactivity response in male offspring hypertensives. Heightened HR, FBF reactivity, and hyperkinetic patterning responses to mental challenge have been identified in healthy, moderately active males with a family history of hypertension.

CHAPTER 5

STUDY II. CARDIOVASCULAR REACTIVITY AND RENAL RESPONSES TO MENTAL CHALLENGE IN HIGHLY AND MODERATELY ACTIVE MALES WITH A FAMILY HISTORY OF HYPERTENSION.

In Study I, enhanced forearm blood flow (FBF) reactivity to mental challenge in the moderately active offspring hypertensives was identified as a possible risk marker for the development of hypertension. Analysis of the cardiovascular patterning responses to mental challenge suggests that enhanced FBF reactivity may be indicative of differences in regional blood flow response. Hollenburg *et al.* (1981) have shown that blood flow to the kidney is significantly reduced during mental challenge in offspring hypertensives. Thus, the skeletal muscle vasodilatory response to stress may be matched by renal vasoconstriction. Activation of the renal α-adrenergic receptors is thought to induce sodium retention through activation of the renin-angiotensin-aldosterone system (RAS) causing renal constriction (DiBona, 1982, 1985). Therefore, if the skeletal muscle vasodilatory response is accompanied by renal vasoconstriction then subjects displaying high levels of FBF reactivity should also be sodium retainers.

A critical factor in the development of hypertension is the failure of the kidneys to maintain blood pressure (BP) within normal limits by excreting sufficient salt and water. However, stress-induced sodium retention may be an important contributor to the pathogenic process, particularly in genetically predisposed individuals. Kohno *et al.* (1997) have shown that the RAS and sympathetic nervous system (SNS) were suppressed (significant reductions in plasma renin and norepinephrine activity) after 4 weeks of exercise training in hypertensive subjects, resulting in reduced renal vascular resistance and filtration fraction. However, no research has investigated the effect of exercise on stress induced sodium retention in

offspring hypertensives. Given that exercise training has been shown to alter renal haemodynamics in hypertensives, Study II was designed to investigate the hypothesis that there will be greater renal vasoconstriction, and thus sodium retention, in moderately active compared with highly active offspring hypertensives during mental challenge.

5.1 Protocol

Eighteen healthy normotensive males with a family history of hypertension were recruited from a student population and from local athletic clubs. The study was approved by a University human ethics committee and all subjects were provided written informed consent before participation. All subjects were screened as described in Chapter 3.

Subjects were required to follow dietary guidelines 24 hr prior to testing (Appendix IIB), which included abstaining from alcohol and caffeine. Dietary guidelines were employed mainly to control for salt intake as this is known to effect the cardiovascular stress reactivity response (Miller *et al.*, 1995). Subjects provided a record of what they had actually consumed and this was later analysed for nutrient content using the computer software package *COMP-EAT* (Bengston Consultants Ltd, 1995). Subjects were also instructed to abstain from rigorous physical activity 24 hr before testing. Two groups comprised of nine moderately active offspring hypertensives (MOD: <40 $kcal.kg^{-1}.d^{-1}$) who were involved with recreational physical activity no more than three times per week and nine highly active offspring hypertensives (HIGH: >40 $kcal.kg^{-1}.d^{-1}$) who were aerobic athletes involved with daily aerobic physical training.

All testing was performed early morning after an overnight fast. The testing was in a quiet, air-conditioned laboratory held at constant room temperature of 24°C with subjects in the supine position.

5.1.1 Baseline

Subjects were instructed to provide a baseline urine sample immediately on awakening on the morning of testing. After 20 min of quiet rest subjects were required to void their bladder. Then a 6-min baseline period of data collection was initiated. This consisted of 3 min of normal breathing and 3 min of paced breathing (10 cycles.min^{-1}). During minutes 6-8 baseline FBF was measured.

5.1.2 Mental Challenge

This consisted of the Stroop word/colour task (Stroop, 1935) for 10 min as described in Chapter 3. Subjects' perceived difficulty of the task, using the Borg 6-20 scale (Borg, 1962), together with mistakes were recorded. Subjects were encouraged to make as few mistakes as possible. FBF was measured during minutes 0-2 and 9-10 of the mental challenge, but all other cardiovascular variables were measured continuously.

5.1.3 Recovery

After the mental challenge there was a 2-min recovery period in the supine position, during which all variables were continuously measured. Then, after a 15-min period of seated upright recovery subjects were instructed to provide another urine sample. Both urine samples were immediately frozen for subsequent analysis.

5.1.4 Maximal oxygen uptake

This was measured at the end of the protocol (see Chapter 3). See Appendix IIC for a detailed protocol of Study II.

5.2 Statistical Analysis

A 2 × 5 repeated measures analysis of variance (ANOVA) was employed to identify changes in cardiovascular variables over time and group differences. The within subject factor comprised of baseline, minutes 0-2, 5-6, and 9-10 of Stroop, and recovery. The between subject factor was the two groups (highly and moderately active). A 2 × 4 repeated measures ANOVA was employed to identify changes in FBF that comprised of four within subjects factors (baseline, minutes 0-2 and 9-10 of Stroop, and recovery).

A dependent *t*-test was employed to identify changes in urinary variables pre and post stressor within each group and an independent *t*-test was used to identify differences in change scores between groups.

Pearson correlation analysis was performed to investigate the relationship between change in urinary variables and heart rate (HR) change during Stroop, change in urinary variables and change in FBF, and change in HR and change in FBF during Stroop.

5.3 Results

5.3.1 Subject Characteristics and 24 hour Dietary Intake

Subject characteristics and 24 hr dietary intake details are displayed in Table 5.1. The HIGH group was significantly older and displayed significantly higher physical activity and $\dot{V}O_{2max}$ values. The HIGH group also displayed significantly lower resting heart rate (RHR). Both groups displayed normotensive resting BP and also normal state anxiety. All subjects adhered to dietary guidelines, although the HIGH group displayed a non-significant trend for higher calorie consumption, which accounted for their significantly greater total salt intake.

Table 5.1. Descriptive characteristics and 24 hour dietary intake details of moderately active (MOD; $n = 9$) and highly active (HIGH; $n = 9$) subjects with family history of hypertension (mean ± *SEM*).

Variable	MOD	HIGH
Age (years)	20.1 ± 0.5	25.3 ± 1.5 *
Body mass (kg)	73.1 ± 2.5	75.1 ± 2.5
Height (cm)	179.6 ± 2.5	182.9 ± 3.0
Body fat %	14.4 ± 1.0	12.6 ± 1.0
Physical activity ($kcal.kg^{-1}.d^{-1}$)	35.0 ± 0.2	45.0 ± 1.8 *
$\dot{V}O_{2max}$ ($ml.kg^{-1}.min^{-1}$)	48.3 ± 1.9	55.3 ± 2.4 *
State anxiety	30.7 ± 2.4	30.8 ± 1.5
RHR ($b.min^{-1}$)	65.4 ± 3.1	49.8 ± 2.9 *
SBP (mmHg)	122.1 ± 3.3	127.8 ± 4.3
DBP (mmHg)	62.4 ± 2.5	60.0 ± 2.8
Calorie consumption (kcal)	1571 ± 121	2002 ± 186
Salt intake ($g.100\ kcal^{-1}$)	0.28 ± 0.03	0.40 ± 0.05
Total salt intake (g)	4.4 ± 0.5	7.7 ± 0.9 *
Total sodium intake (mg)	1724 ± 205	3025 ± 354 *

* significant difference between groups.

5.3.2. Response to Stroop Mental Challenge

During the Stroop mental challenge there was no significant differences in perceived task difficulty (*mean ± SEM*: 14.6 ± 0.6 versus 14.3 ± 0.4) or mistakes (70 ± 12 versus 56 ± 14) for the MOD and HIGH groups respectively.

5.3.2.1. Central cardiovascular responses. For HR there was a significant main effect over time [F (4, 64) = 10.79, P<0.05], but no interaction or between subject effects. HR was significantly increased during the first 2 min of Stroop in comparison with baseline (unpaced breathing). See Figure 5.1a and Table 5.2.

There was no significant main effect over time within subjects or between subject effects for cardiac output (CO) [F (4, 64) = 0.82, P>0.05]. See Figure 5.1b and Table 5.2.

There was a significant main effect over time within subjects for stroke volume (SV) [F (4, 64) = 13.77, P<0.05], and between subject effects [F (1, 16) = 6.43, P<0.05], but no group interaction over time. SV was significantly reduced during all stages of the Stroop with respect to baseline (see Figure 5.1c).

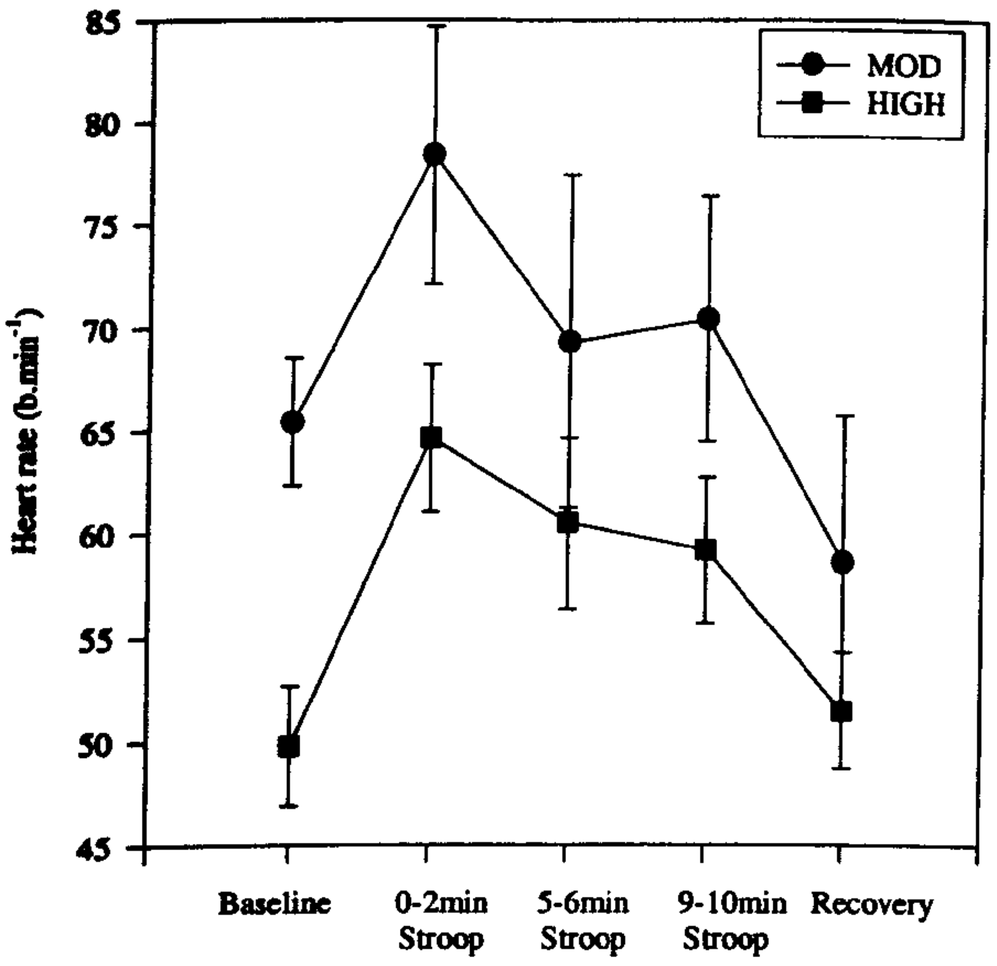


Figure 5.1a. Heart rate response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

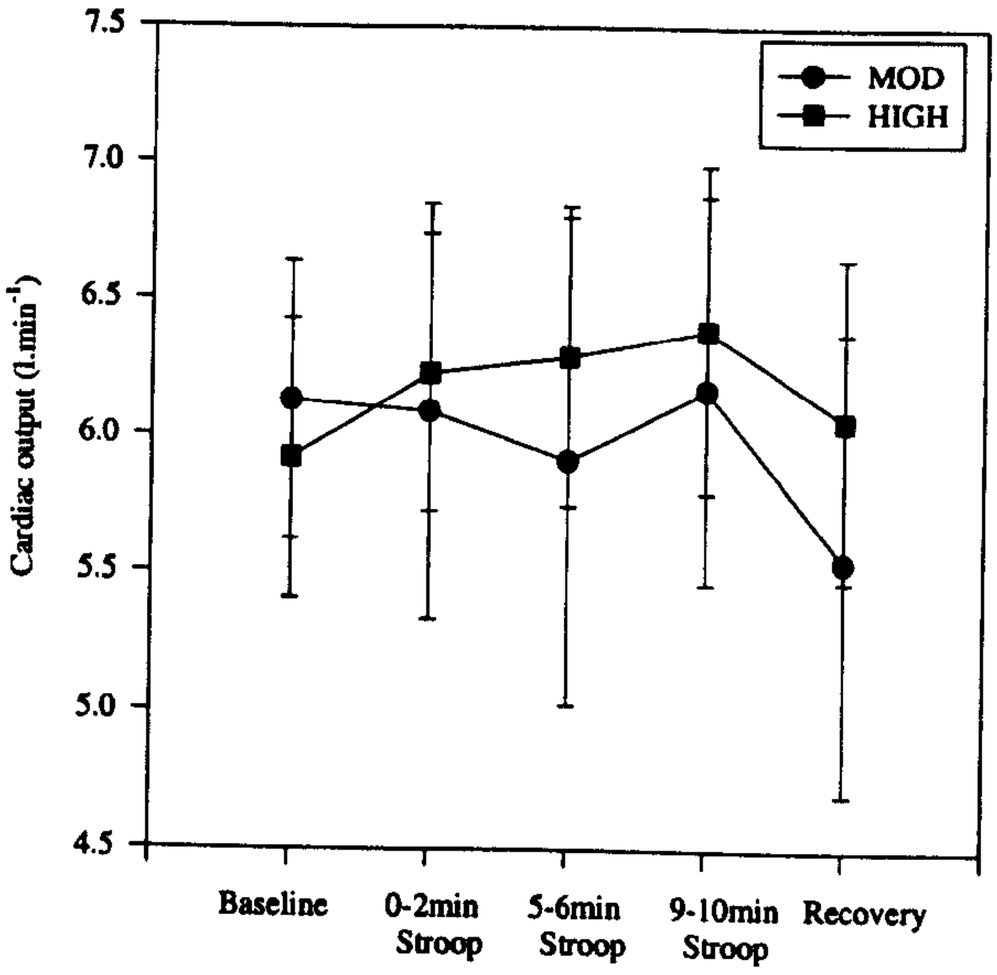


Figure 5.1b. Cardiac output response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

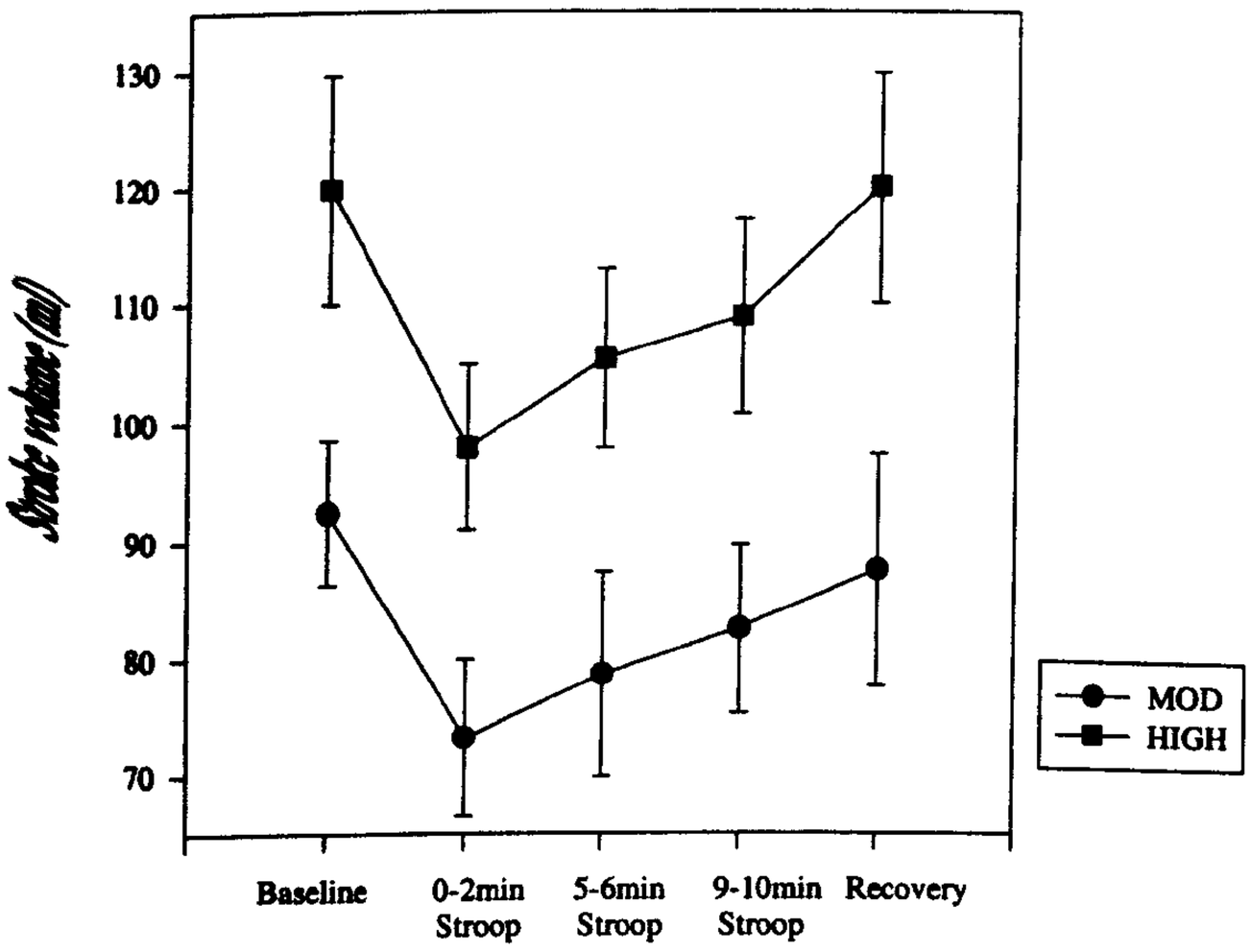


Figure 5.1c. Stroke volume response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

5.3.2.2 Cardiac autonomic responses. There was a significant main effect over time within subjects for time series analysis of heart period variability (HPV_{ts}) in the high frequency domain (0.12-0.4 Hz) [F (5, 80) = 45.8, P<0.05], but no interaction or between subject effects. HPV_{ts} was significantly reduced during all stages of the Stroop and recovery from Stroop in comparison with baseline (paced breathing). See Figure 5.2a and Table 5.2

There a significant main effect over time for HPV_{ts} in the medium frequency domain (0.07-0.11 Hz) [F (5, 80) = 11.04, P<0.05], but no interaction or between subject effects. HPV_{ts} was significantly reduced during minutes 0-3 and 5-8 of the Stroop in comparison with baseline (paced breathing). See Figure 5.2b and Table 5.2.

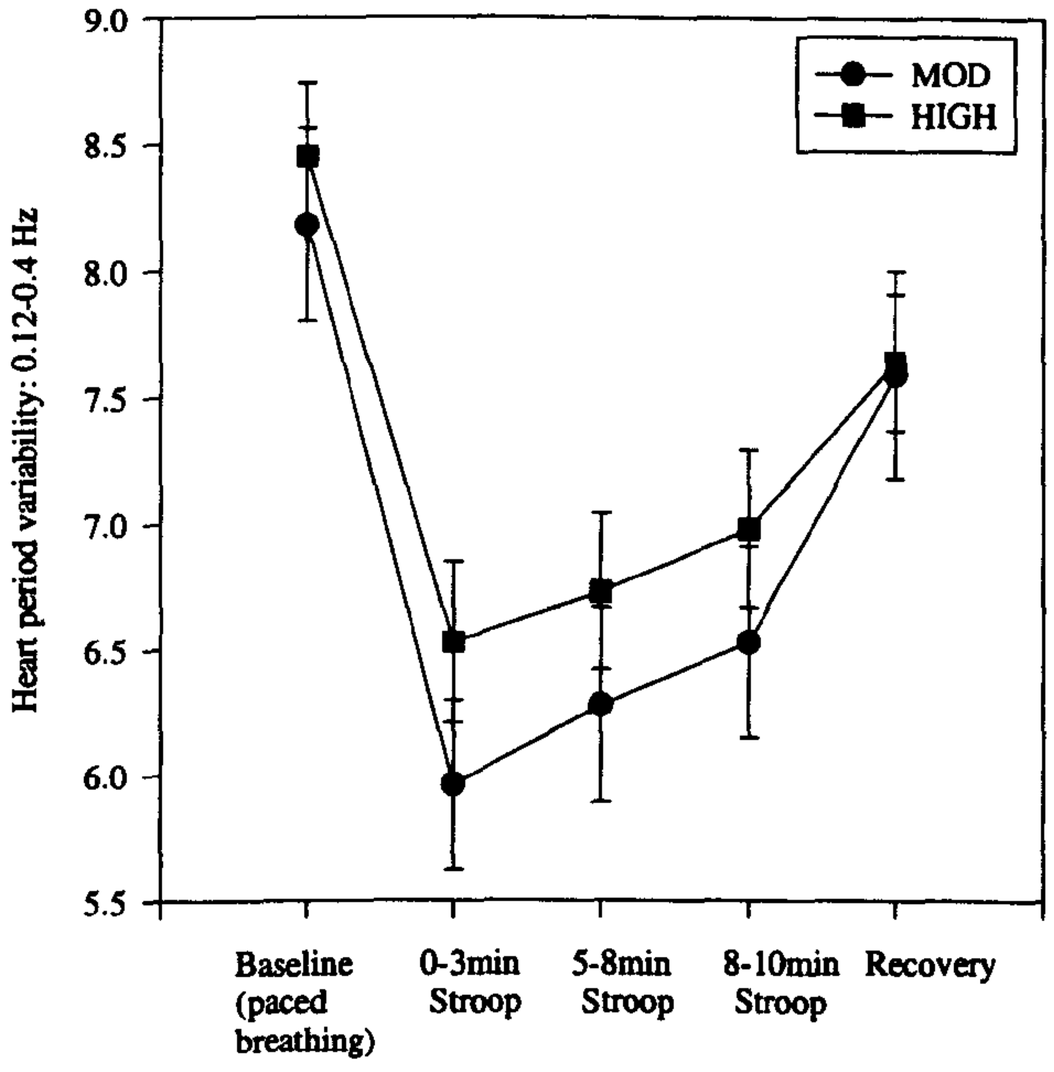


Figure 5.2a. Heart period variability response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

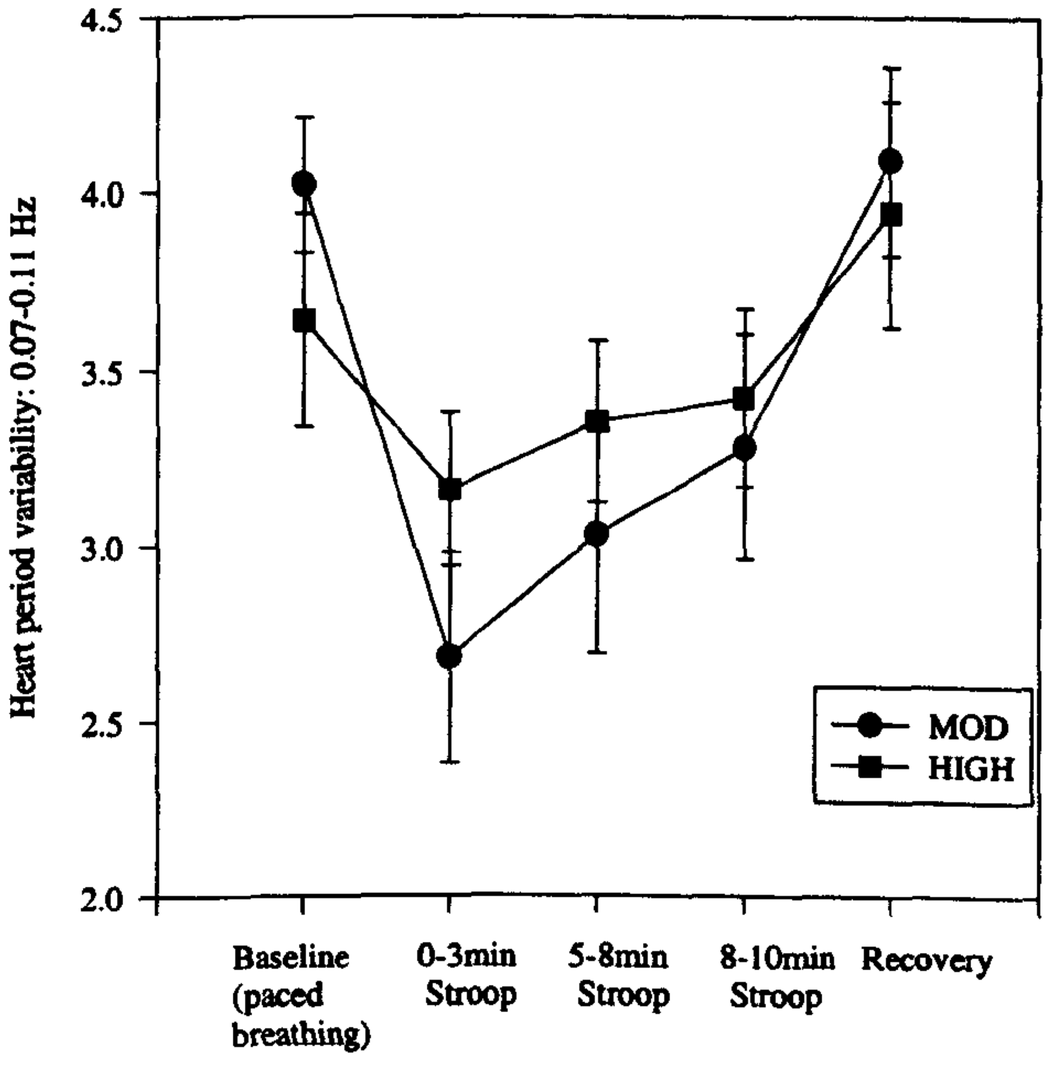


Figure 5.2b. Heart period variability response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

5.3.2.3 Cardiac contractility. There was a significant main effect over time for pre-ejection period (PEP) [F (4, 64) = 4.27, P<0.05], but no interaction or between subject effects. PEP was significantly reduced during the first 2 min of the Stroop in comparison with baseline. Although not significant, there was a trend for greater decreases in PEP during the Stroop in the MOD group in comparison with the HIGH (see Figure 5.3a and Table 5.2).

There a significant main effect over time for left ventricular ejection time (LVET) [F (4, 64) = 20.81, P<0.05], and between subject effects [F (1, 16) = 12.54, P<0.05], but no significant interaction over time. LVET was significantly reduced throughout the Stroop in comparison with baseline (see Figure 5.3b and Table 5.2).

There were no significant effects for PEP/LVET (PL) ratio over time (see Figure 5.3c and Table 5.2).

There was a significant main effect [F (4, 64) = 3.84, P<0.05] and interaction over time for Heather Index (HI) [F (4, 64) = 2.69, P<0.05]. HI was reduced during the first two minutes of Stroop, although after applying Bonferoni adjustments this reduction was no longer significant. However, the HIGH displayed greater decreases in HI during the first 2 min of Stroop in comparison with the MOD group (see Figure 5.3d and Table 5.2).

Because both groups displayed comparatively constant loading conditions throughout (i.e., a similar trend in SV), the trend for a greater reduction in PEP during Stroop in the MOD group suggests a greater level of cardiac sympathetic activation in the MOD group.

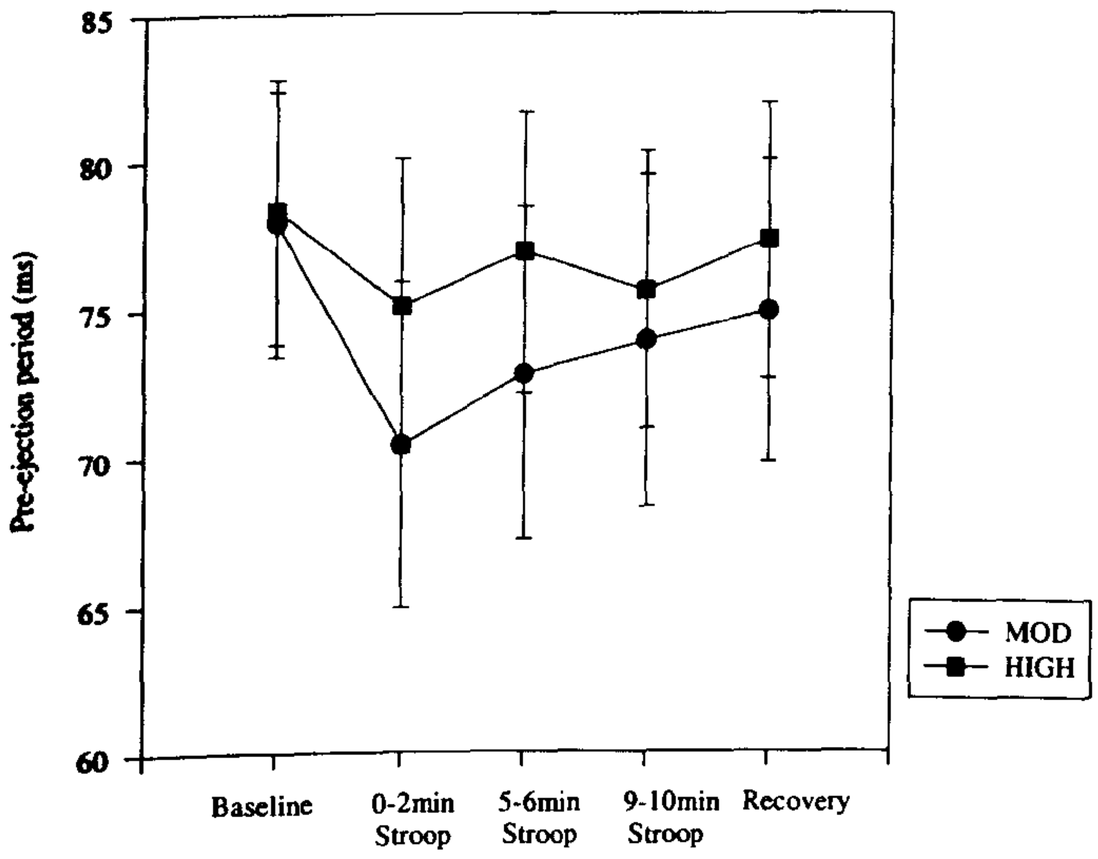


Figure 5.3a. Pre-ejection period in response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

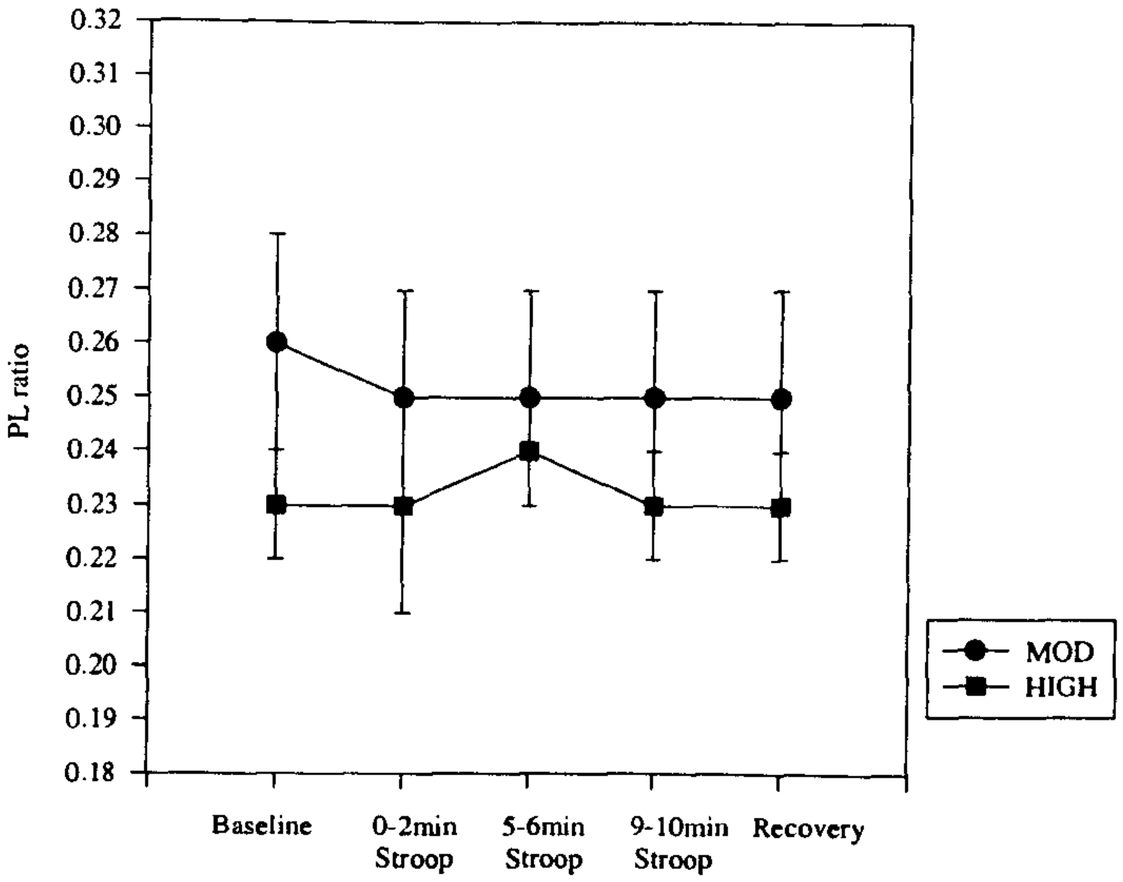


Figure 5.3c. PEP/LVET ratio in response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

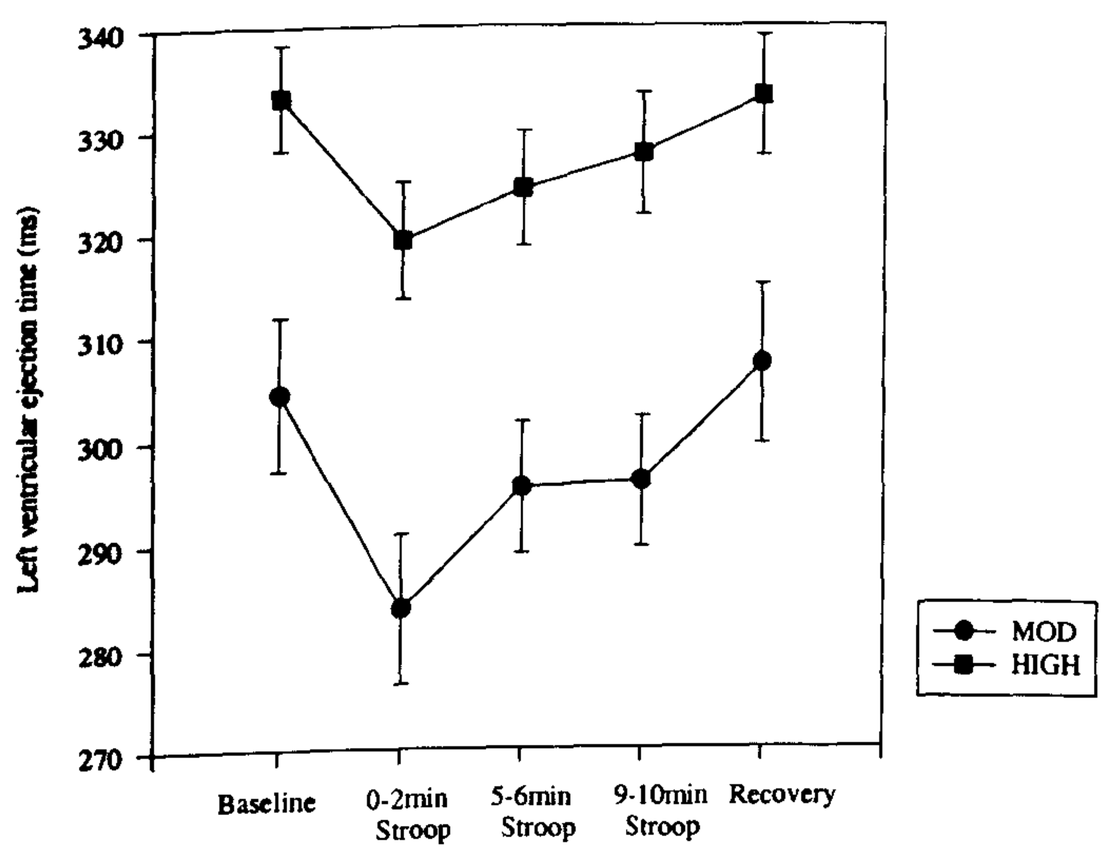


Figure 5.3b. Left ventricular ejection time in response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

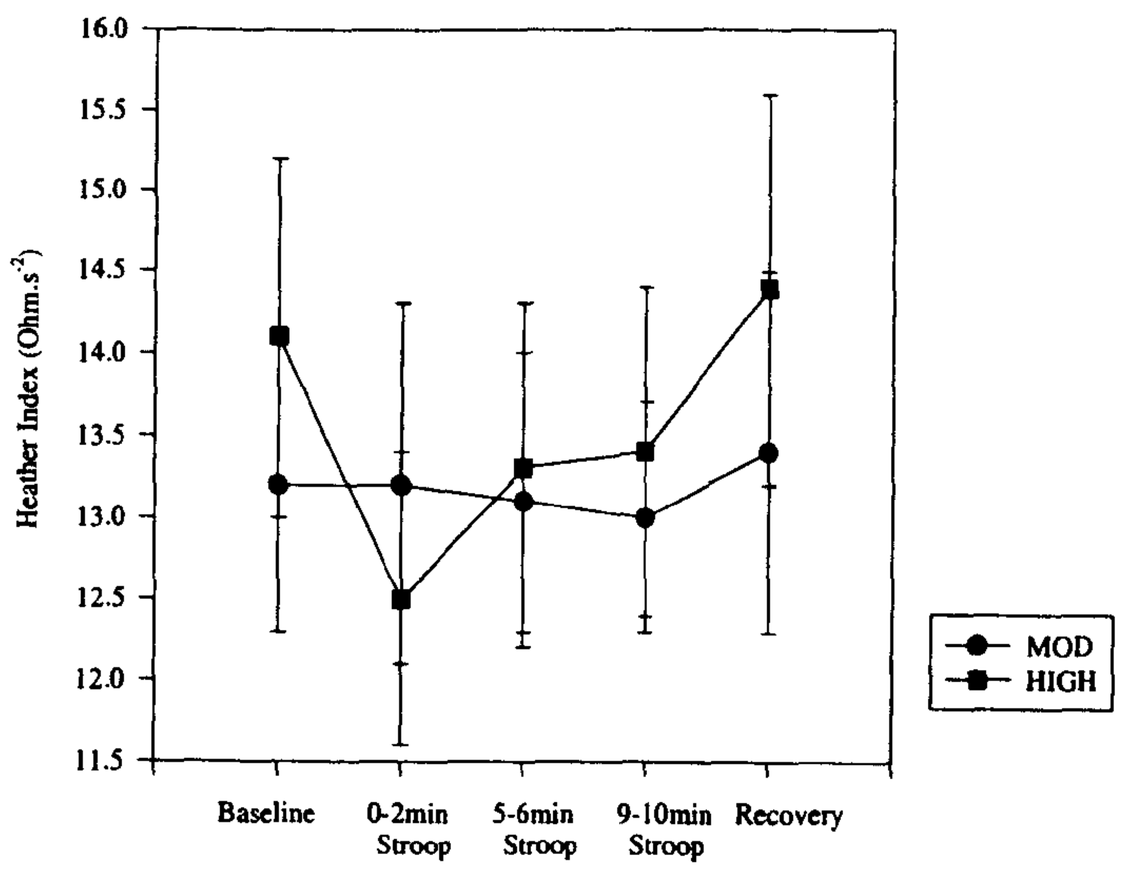


Figure 5.3d. Heather Index in response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

5.3.2.4 Blood pressure. There was a significant main effect over time within subjects for systolic blood pressure (SBP) [F (4, 64) = 41.97, P<0.05], diastolic blood pressure (DBP) [F (4, 64) = 71.01, P<0.05], and mean arterial blood pressure (MAP) [F (4, 64) = 60.95, P<0.05], but no interaction or between subject effects. SBP, DBP, and MAP were elevated during all stages of Stroop and recovery in comparison to baseline (see Figures 5.4a-c and Table 5.2).

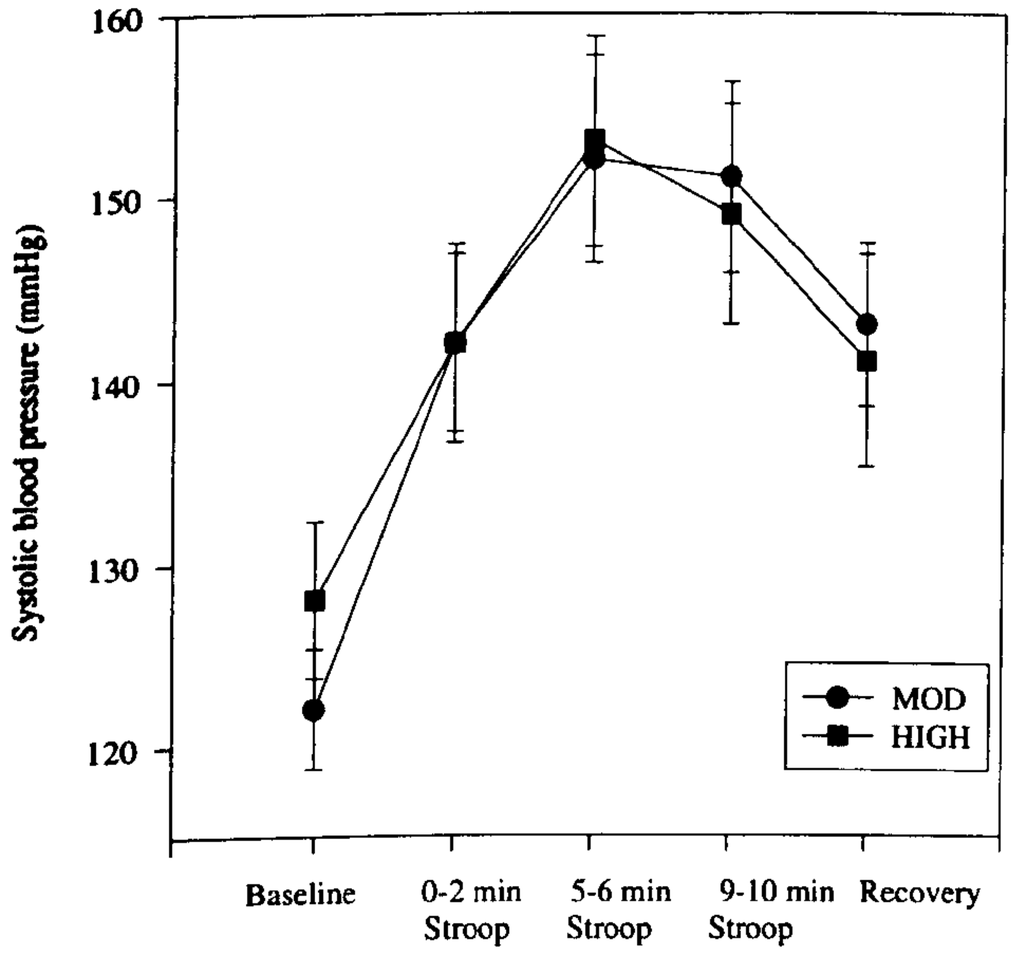


Figure 5.4a. Systolic blood pressure response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

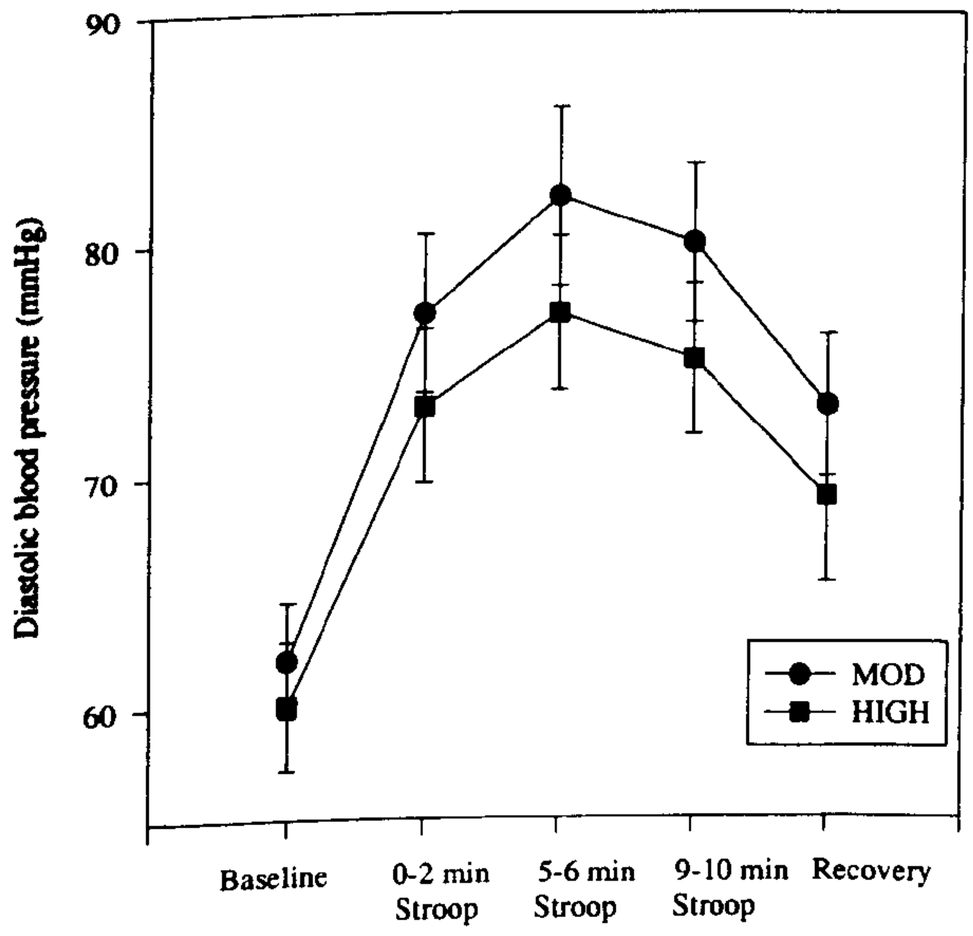


Figure 5.4b. Diastolic blood pressure response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

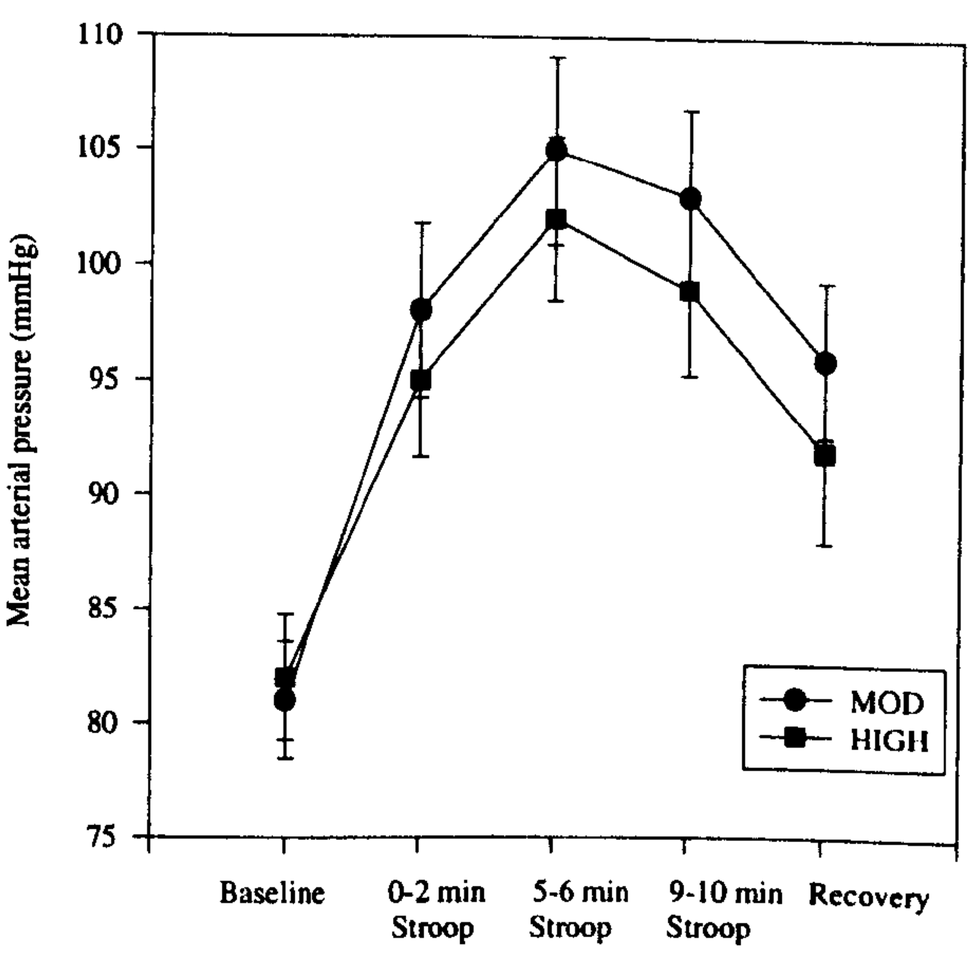


Figure 5.4c. Mean arterial pressure response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

5.3.2.5 Peripheral vascular responses. There was a significant main effect within subjects for total peripheral resistance (TPR) [F (4, 64) = 10.53, P<0.05], but no interaction or between subject effects. TPR was significantly elevated during all stages of Stroop and recovery in comparison to baseline (see Figure 5.5a and Table 5.2).

There was a significant main effect [F (3, 48) = 50.75, P<0.05], and interaction [F (3, 48) = 7.3, P<0.05] over time for within subject factors for FBF. FBF was significantly increased during both the first and last 2 min of Stroop in comparison with baseline. Subsequent analysis revealed that during the first 2 min of Stroop the MOD group displayed a significantly greater increase in FBF compared with HIGH [F (1, 16) = 7.9, P<0.05, ES = 1.25] (see Figure 5.5b and Table 5.2).

There was a significant main effect for forearm vascular resistance (FVR) [F (3, 48) = 20.39, P<0.05], and a trend for an interaction over time [F (3, 48) = 2.69, P= 0.09]. FVR was significantly reduced during both the first and last 2 min of Stroop in comparison with baseline. Also, during the first 2 min of Stroop the MOD group displayed a significantly greater reduction in FVR compared with HIGH [F (1, 16) = 9.09, P<0.05] (see Figure 5.5c and Table 5.2).

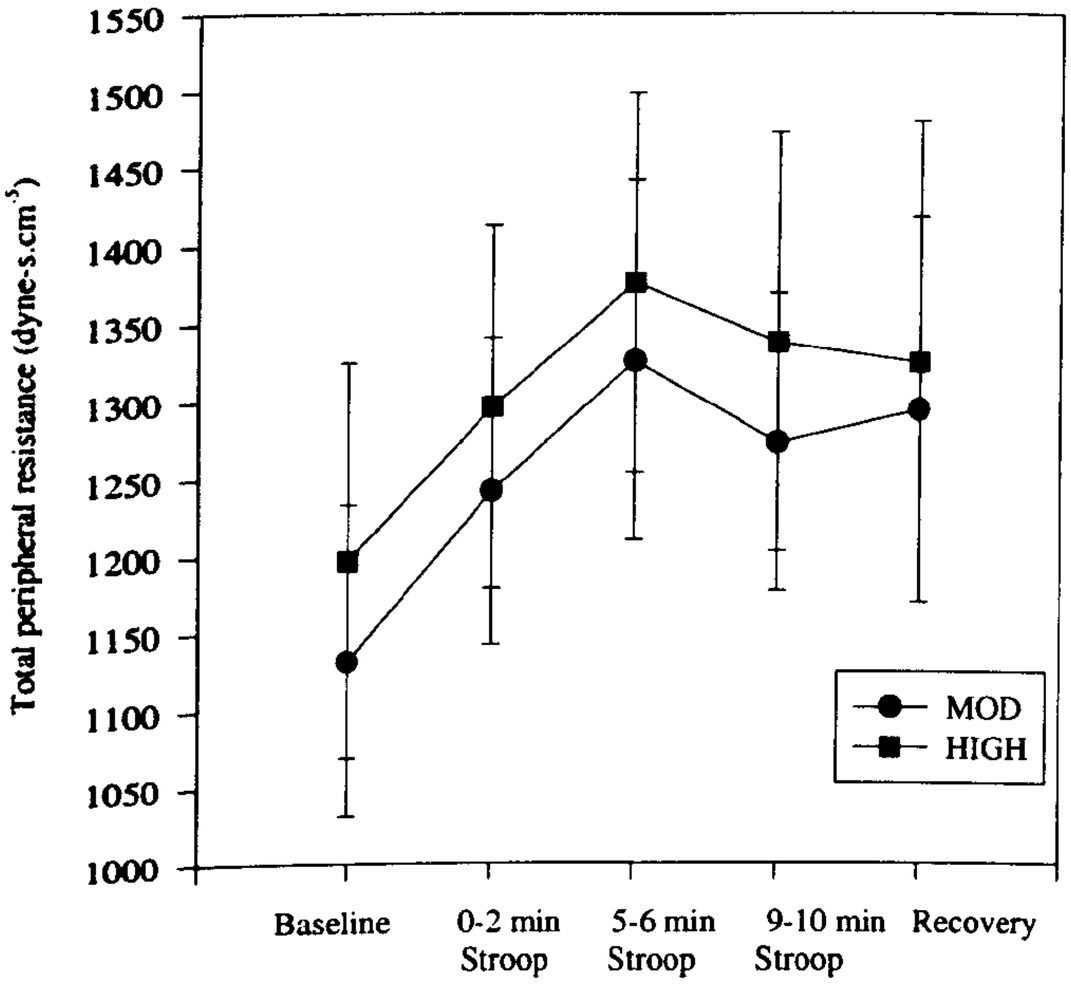


Figure 5.5a. Total peripheral resistance response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

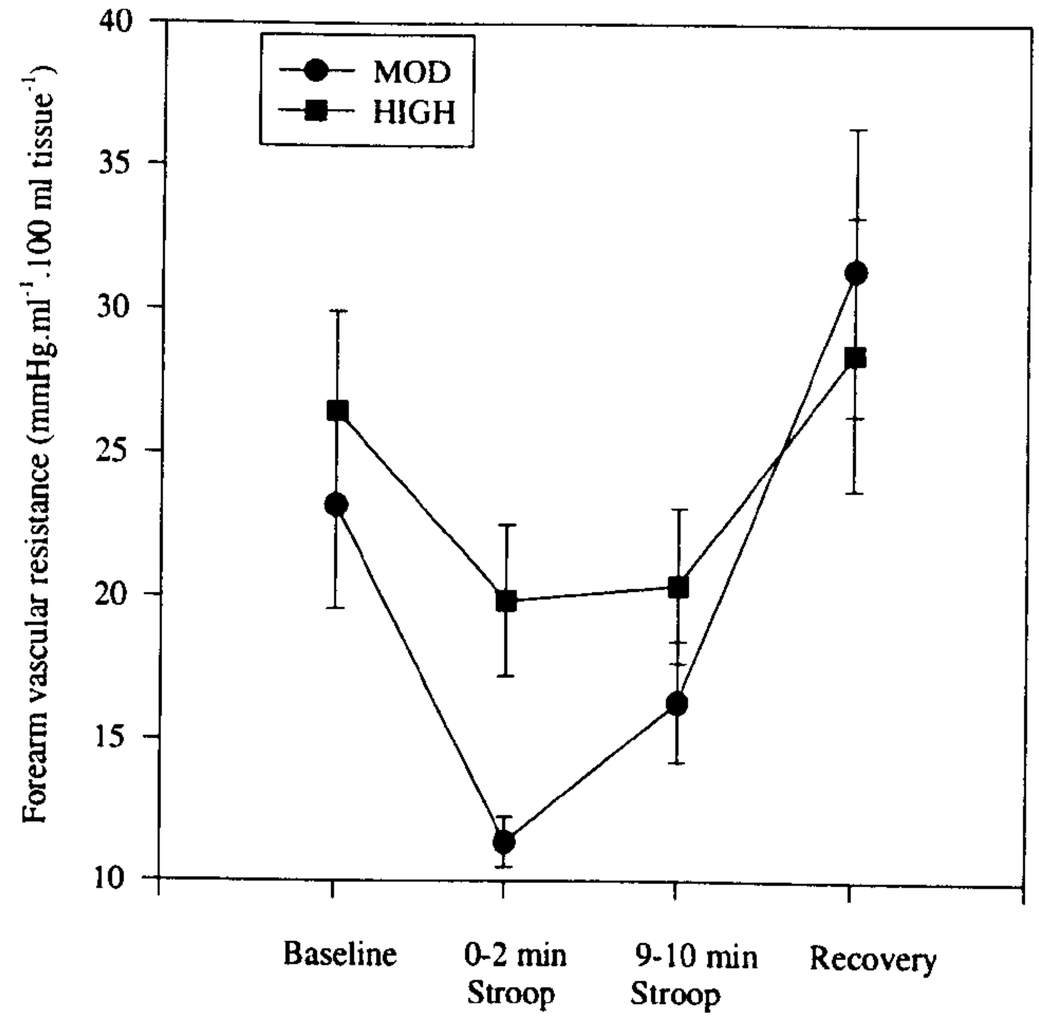


Figure 5.5c. Forearm vascular resistance response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives.

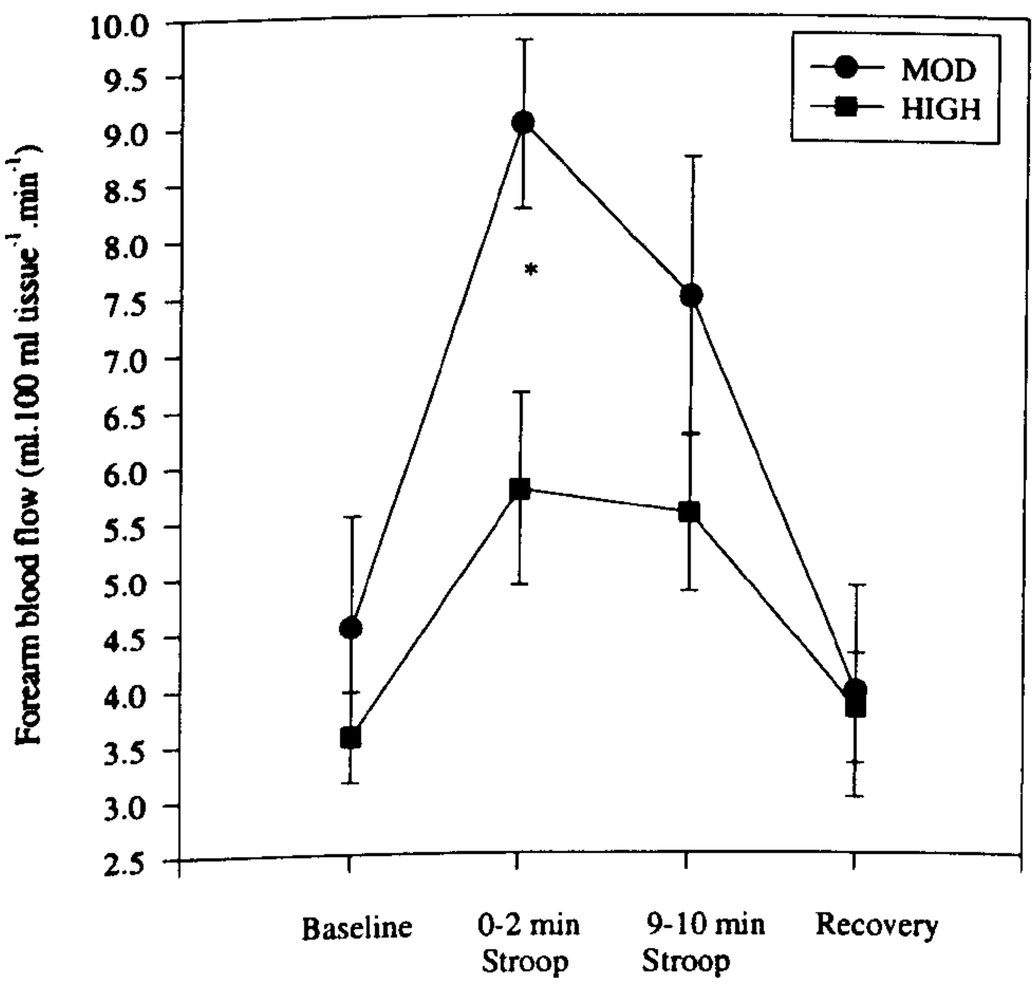


Figure 5.5b. Forearm blood flow response to Stroop mental challenge in highly (HIGH) and moderately active (MOD) offspring hypertensives. * Significantly different change between groups from baseline.

5.3.2.6 Renal responses. There was a significant increase in urinary sodium [t (1, 17) = 3.65, P<0.05] and potassium levels [t (1, 17) = 4.77, P<0.05], post stress in comparison with baseline. The change in sodium and potassium levels from pre to post stressor were, however, not significantly different between groups (see Figures 5.6a and b).

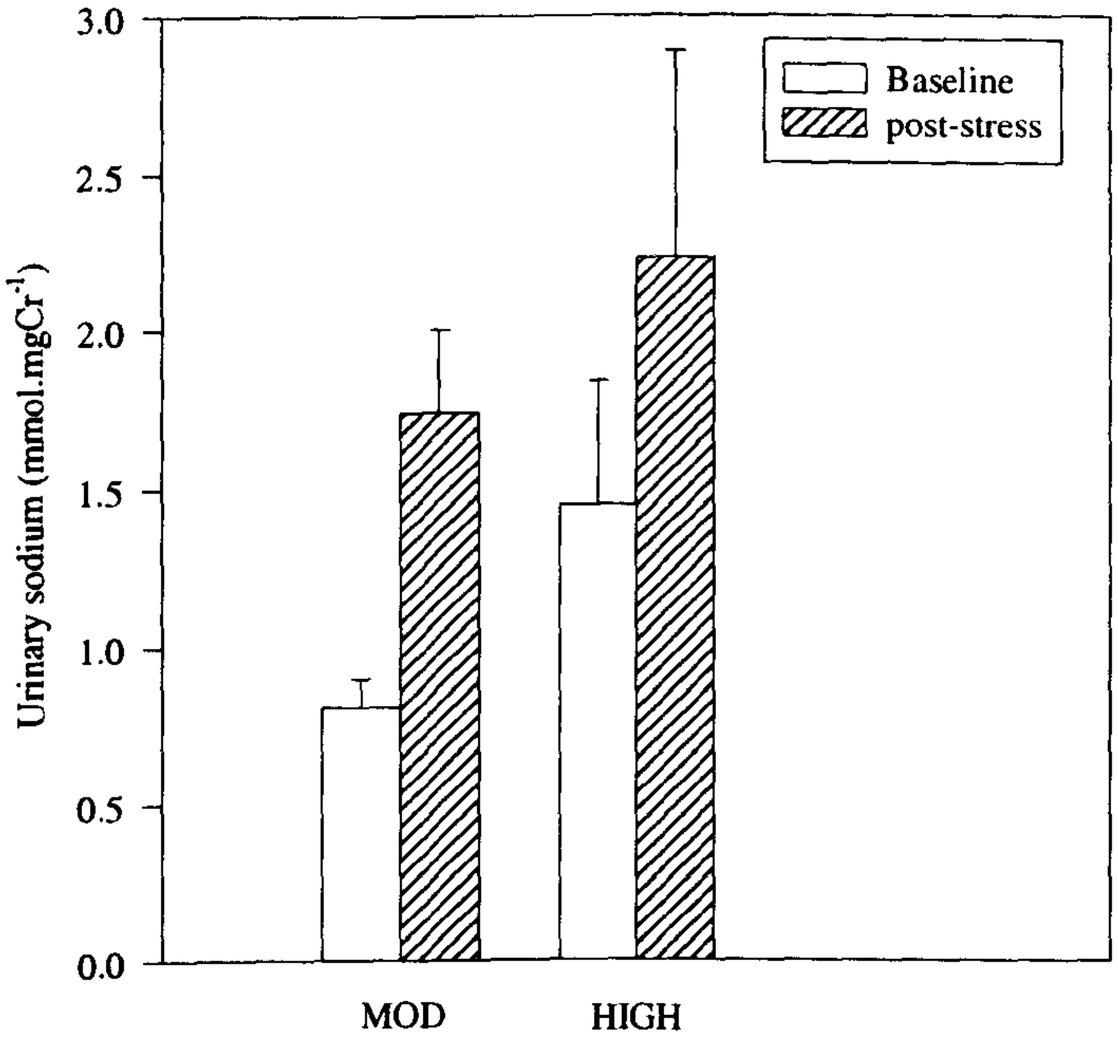


Figure 5.6a. Urinary sodium pre and post Stroop mental challenge in highly (HIGH) and moderately (MOD) active offspring hypertensives.

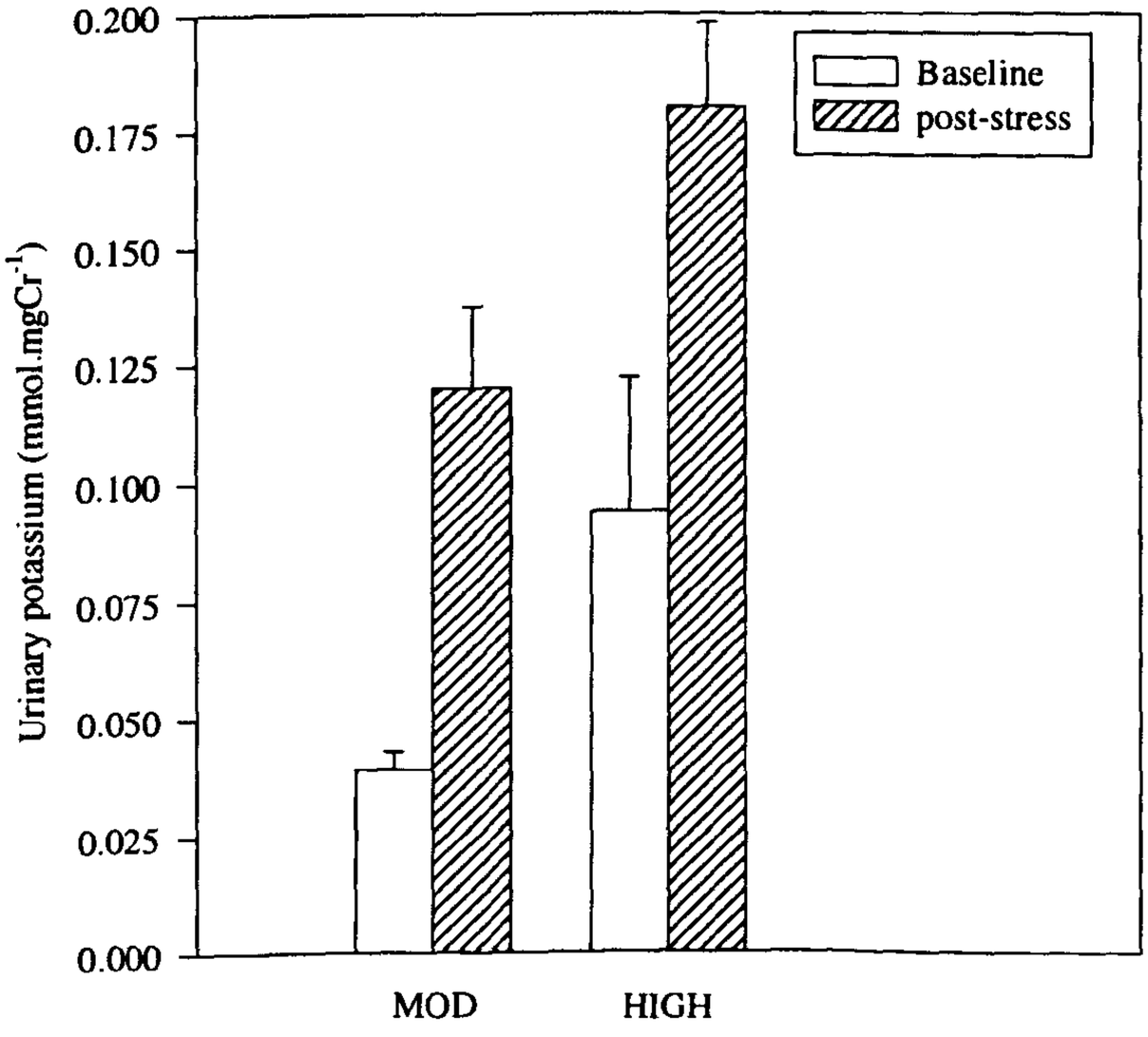


Figure 5.6b. Urinary potassium pre and post Stroop mental challenge in highly (HIGH) and moderately (MOD) active offspring hypertensives.

5.3.2.7 Pearson correlations. There was no significant relationship between urinary sodium change and HR change (r = -0.33, P>0.05) or urinary potassium change and HR change (r = -0.24, P>0.05). Nor was there a relationship between urinary sodium change and FBF change (r = -0.09, P>0.05) or urinary potassium change and FBF change (r = -0.11, P>0.05). There was, however, a significant correlation (r = 0.75, P<0.01) between HR change and FBF change during the first 2 min of the Stroop mental challenge (see Figure 5.7).

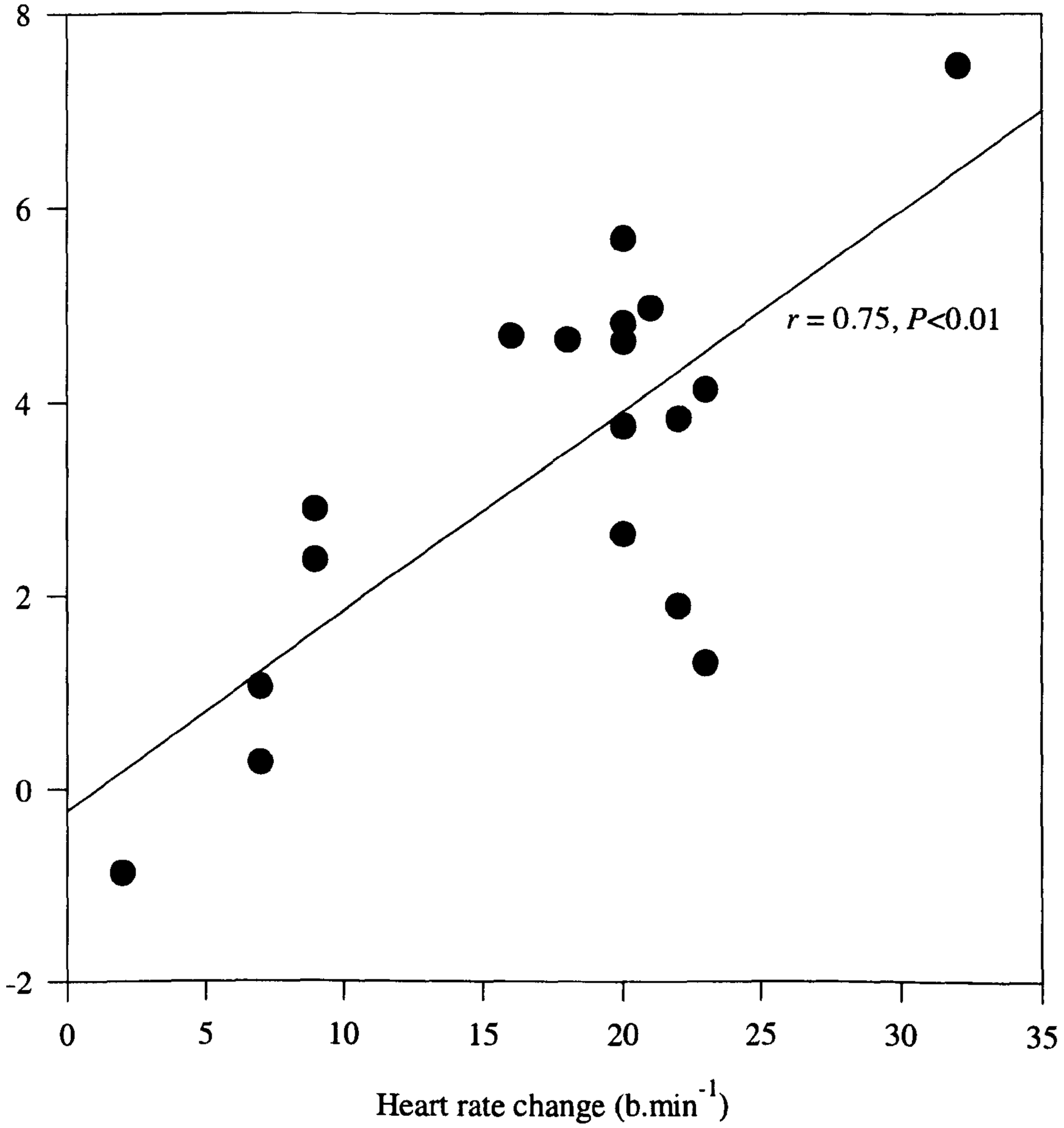


Figure 5.7. Relationship between heart rate change and forearm blood flow change during the first two minutes of Stroop mental challenge, with respect to baseline, in male offspring hypertensives.

Table 5.2. Response to Stroop mental challenge in moderately active (MOD; $n = 9$) and highly active (HIGH; $n = 9$) males with family history of hypertension (mean ± *SEM*).

Variable	Condition									
	Baseline		Stroop (0-2 min)		Stroop (4-6 min)		Stroop (8-10 min)		Recovery	
	MOD	HIGH	MOD	HIGH	MOD	HIGH	MOD	HIGH	MOD	HIGH
HR ($b.min^{-1}$)	67.6±3#	50.7±3#	78.4±6	64.6±4	69.3±8	60.5±4	70.4±6	59.2±4	58.6±7	51.5±3
SV (ml)	92.4±6	119.8±10	73.2±7	98.0±7	78.6±9	105.5±8	82.5±7	108.9±8	87.5±9	120.0±10
CO ($l.min^{-1}$)	6.1±.5	5.9±.5	6.1±.8	6.2±.5	5.9±.9	6.3±.6	6.2±.7	6.4±.6	5.5±.8	6.1±.6
HPV_{ts} (.12-.4 Hz)	8.2±.3#	8.4±.3#	5.9±.3	6.5±.3	6.3±.3	6.7±.3	6.5±.3	7.0±.3	7.6±.3	7.6±.4
HPV_{ts} (.07-.11 Hz)	4.0±.2#	3.6±.3#	2.7±.3	3.2±.3	3.0±.2	3.4±.2	3.3±.3	3.4±.3	4.1±.3	3.9±.4
PEP (ms)	77.9±5	78.3±5	70.4±6	75.1±5	72.8±6	76.9±5	73.9±6	75.6±5	74.9±5	77.3±5
LVET (ms)	304.4±7	333.0±5	283.6±7	319.1±6	295.3±6	324.1±6	295.9±6	327.5±6	307.1±8	333.1±6
PL ratio	.26±.02	.23±.01	.25±.06	.23±.04	.25±.02	.24±.01	.25±.02	.23±.01	.25±.02	.23±.01
HI ($Ohm.s^{-2}$)	13.2±1	14.1±1	13.2±1	12.5±1	13.1±1	13.3±1	13.0±1	13.4±1	13.4±1	14.4±1
SBP (mmHg)	122.1±3	127.8±4	142.3±5	142.6±5	152.0±6	153.4±6	151.4±5	149.5±6	143.2±5	141.1±6
DBP (mmHg)	62.4±3	60.0±3	77.3±4	73.0±3	82.9±4	77.4±3	80.5±3	75.8±3	73.3±3	69.7±4
MAP (mmHg)	81.2±3	82.4±5	98.8±4	95.6±3	105.1±4	102.6±4	103.4±4	99.1±4	96.3±4	92.1±4
TPR ($dyne\text{-}s.cm^{-5}$)	1132±101	1197±128	1242±99	1296±117	1326±116	1376±122	1273±96	1338±135	1294±124	1325±155
FBF ($ml.100\ ml\ tissue^{-1}.min^{-1}$)	4.5±1	3.6±.4	9.0±.8	5.8±.9*	-	-	7.5±1	5.6±.7	4.0±.9	3.8±.5
FVR ($mmHg.\ ml^{-1}.100\ ml\ tissue^{-1}$)	23.2±4	26.5±3	11.4±.9	19.9±3*	-	-	16.3±2	20.4±3	31.4±5	28.5±5

* significant difference in change between groups in comparison with baseline.

baseline cardiac data for paced breathing.

5.4 Discussion

The purpose of Study II was to investigate the association between physical activity level and cardiovascular and renal responses to mental challenge in offspring hypertensives. It was predicted that if exaggerated FBF during mental challenge was due to a renal vasoconstrictor response then high forearm vascular responsiveness should be characterised by sodium retention. Because the moderately active offspring hypertensives displayed greater FBF reactivity to mental challenge it was expected that this group would also retain sodium. However, this was not the case, despite similar CO and BP responses to mental challenge between the high (MOD group) and low FBF reactors (HIGH group). This suggests there may still be regional blood flow differences in other vascular beds. It is possible that all of the major skeletal muscle vascular beds do not react in a similar way to mental challenge. However, Halliwill (2001) has suggested there is a strong correlation between the skeletal muscle vascular reactivity of the forearm and calf. Research using spontaneously hypertensive rats (SHR) and normotensive controls, the Wistar-Kyoto (WKY), has shown that although both strains demonstrate similar BP changes to the defence response, regional blood flow changes are different (Kirby, Woodworth, Woodworth, & Johnson, 1991). Specifically, SHR demonstrated increases in mesenteric vascular resistance that appeared to be offset by more pronounced decreases in hindquarter vascular resistance (increased skeletal muscle vasodilatation).

5.4.1 Vascular Stress-reactivity Mechanism

The finding that HR change and FBF during mental challenge were significantly correlated supports the notion that one mechanism underlies cardiac and vascular reactivity. It is plausible that this mechanism may involve sympathetic activation of β-1 and β-2 adrenergic receptors producing increased HR and skeletal

muscle vasodilatation, respectively. This is supported by the findings of Miller and Ditto (1991) that strongly implicate the SNS in the exaggerated cardiovascular response to stress in offspring hypertensives. Their study employed the use of selective pharmacological blockade, a β-1 adrenergic blocker, and an α-1 adrenergic blocker. The study compared HR and FBF response between offspring hypertensives and controls during a 1-hr active coping psychological stressor under a placebo and two drug conditions. Under the placebo condition the offspring hypertensives demonstrated exaggerated HR and FBF responses to the stressor. Under the β-1 adrenergic blocking condition only differences in HR response were abolished. Under the α-1 adrenergic blocker the responses were similar to that observed under the placebo condition for the first 15-min although during the last 15-min, the α-blocker eliminated the rise in FVR observed in offspring hypertensives under the placebo condition. These results suggest that the initial forearm vasodilatation response to stress and the reductions in FVR are reinforced by β-2 adrenergic or cholinergic activity and that later increases in FVR may reflect increasing α-adrenergic activity. Furthermore, Halliwill *et al.* (1997) examined skeletal muscle vasodilatation to mental stress in order to determine the extent to which this response was due to sympathetic withdrawal, active neurogenic vasodilatation, or β-adrenergically mediated vasodilatation. Firstly, they found that muscle sympathetic nerve activity to the forearm was inhibited during mental stress (a 2.5-min Stroop task), suggesting that sympathetic vasoconstrictor withdrawal may contribute to the vasodilatation response. However, the vasodilatation during mental stress continued to occur after either selective blockade of α-adrenergic neurotransmission or local anaesthetic blockade of the stellate ganglion. Also, after administration of propanolol (β-2 blocker) the vasodilatation response to stress was reduced but not completely abolished. Thus, the

authors concluded that sympathetic withdrawal, through a reduction in discharge of norepinephrine from the autonomic nervous system, might mediate the initial vasodilatation. Then the response could be further augmented by both epinephrine, secreted from the adrenal gland, acting via β-2 adrenergic receptors and also activation of local mechanisms that release nitric oxide. Such local mechanisms may include the release of acetylcholine from selected endothelial cells stimulated mechanically by increases in blood flow and rises in arterial BP. The locally released acetylcholine is then thought to act on muscarinic receptors and cause nitric oxide release producing vasodilatation (Dietz *et al.*, 1994).

5.4.2 Exercise-induced Reactivity Lowering Mechanism

Differences in sympathetic withdrawal, β-2 adrenergic receptor activation, and/or local vasodilatation mechanisms may explain the difference in FBF reactivity to mental challenge between the moderately and highly active offspring hypertensives. However, it is interesting to note that the forearm vasodilatation response was only significantly different between the groups during the first 2-min of the mental challenge. This, therefore, suggests that differences in the response are more likely to be due to sympathetic withdrawal and β-2 adrenergic mechanisms because local mechanisms are thought to sustain the response later on. Results from animal studies show that after an acute bout of exercise vascular responsiveness was reduced (Howard & DiCarlo, 1992). Using vasoactive agonists infused into the hindlimb of the conscious rabbit, blood flow responses in the isolated hindlimb were markedly reduced following a bout of treadmill exercise to exhaustion. The authors suggested that this might be due to an exercise induced down regulation of α and/or β-adrenergic receptors. Furthermore, longitudinal studies (Duncan *et al.*, 1985; Jennings *et al.*, 1986; Meredith *et al.*, 1991; Urata *et al.*, 1987) have consistently

shown that endurance training reduces plasma catecholamine concentration. However, because plasma catecholamine levels represent a measure of average sympathetic neural activity, it is difficult to determine whether central, peripheral, or local mechanisms are primarily or secondarily responsible for the changes. Studies employing methods to measure post-ganglionic sympathetic nerve traffic have suggested that the reduction in sympathetic nervous activity from training originates from a central effect of training (Grassi *et al.*, 1994).

Therefore, the mechanism responsible for a possible exercise induced vascular stress reactivity lowering effect may be a reduction in the sympathetic withdrawal response to stress. Also a down regulation of β-2 adrenergic receptors and/or reductions in sympatho-adrenal activation, reducing epinephrine discharge, thus reducing the β-2 adrenergic vasodilatation response. Evidence from the spontaneously hypertensive rat model (Kirby *et al.*, 1991) suggests that the enhanced β-2 adrenergic vasodilatation in the SHR during the defence response is due to an increased release of epinephrine as opposed to greater sensitivity of the receptors. Research studying plasma catecholamine concentration during mental stress in human offspring hypertensives also supports findings from the SHR study. Falkner, Onesti, and Angelakos (1979) have shown that post-stress plasma catecholamines were higher in offspring hypertensives compared with controls. Also, Horikoshi *et al.*, (1985) found that offspring hypertensives who were high BP responders to mental stress also displayed significantly higher levels of epinephrine throughout the stress.

5.4.3 Renal Responses to Stress

That sodium retention was not displayed in the offspring hypertensives recruited for the present study is in contrast with the findings of Light *et al.* (1983) who found that out of a sample of 13 offspring hypertensives, those who displayed

high HR reactivity to mental challenge (n = 7) had reductions in sodium and water excretion of 27% and 35% respectively. This was in comparison with the low HR reactors with family history of hypertension (n = 6) who demonstrated increases in sodium and fluid excretion of 4%, and individuals with no family history demonstrating 8% increases. Given the high correlation between HR reactivity and sodium retention (r = 0.64, P< 0.05) in the Light *et al* study, a common mediation by the SNS for the cardiac and renal reactivity responses was suggested. This relationship has also been shown in the spontaneously hypertensive rat where renal denervation reduces sodium retention and delays the pathogenic process (Winternitz *et al.*, 1980). There are a number of reasons to explain why subjects in the present study reacted in a similar manner to the low risk group in the Light study (i.e., displayed sodium excretion responses to stress), despite the presence of significant cardiac reactivity in the present subjects. Firstly, although Light *et al* employed a similar type of mental stress (cognitive processing task), their task lasted for a period of 1 hr compared with 10 min in the present study. Miller and Ditto (1991) demonstrated that during an extended 1-hr active-coping stressor a pattern of increasing vascular resistance was observed that is thought to be due to increased α-adrenergic involvement. Thus, extended periods of stress may be required to produce renal vasoconstriction responses and sodium retention. Secondly, because all subjects in the present study were physically active, a moderate level of physical activity may be adequate to reduce a familial tendency to retain sodium. It should be noted that subjects in the moderately active group were in fact all physically fit with an average $\dot{V}O_{2max}$ of 47.88 $ml.kg^{-1}.min^{-1}$. Lastly, in another study (Parfrey, Wright, & Ledingham, 1981) that investigated the effect of prolonged isometric exercise on renal excretion of sodium and potassium, there were no differences in this response

between offspring hypertensives and controls. Therefore, because sodium retention following isometric exercise is seen in hypertensive patients, it is possible that the sodium retention response to stressors is a consequence of, rather than a predisposing factor to hypertension.

5.4.4 Summary

Both the highly and moderately active offspring hypertensives have displayed a sodium excretion response to stress. Although neither group appear to have demonstrated disturbed renal responses during mental challenge, which has previously been identified as a significant risk marker for hypertension development, the moderately active group demonstrated an enhanced FBF reactivity response to mental challenge in comparison with highly active offspring hypertensives. Repeated episodes of a hyper-reactive vascular response to stress has in itself been linked to the development of hypertension through a vascular re-modelling process (Folkow, 1978). Thus physical activity level may be associated with vascular reactivity to a laboratory stressor in offspring hypertensives. That differences in renal response to mental challenge between highly and moderately active groups have not been observed suggests that either a moderate level of physical activity may alleviate familial abnormalities in renal functioning, or that physical activity level is not associated with renal responses to stress in offspring hypertensives.

CHAPTER 6

STUDY III. THE EFFECT OF ACUTE EXERCISE ON CARDIOVASCULAR RESPONSES DURING RECOVERY AND MENTAL CHALLENGE IN MALES WITH A FAMILY HISTORY OF HYPERTENSION.

Studies I and II have provided strong evidence for an association between physical activity and forearm blood flow (FBF) reactivity to mental challenge. However, in order to infer a causal relationship between exercise and stress reactivity Study III has been designed to investigate the short term effects of acute exercise on the cardiovascular stress reactivity response. Previous researchers have documented the phenomenon of post-exercise hypotension as a possible blood pressure lowering mechanism of exercise (Bennett *et al.*, 1984; Floras *et al.*, 1989; Hagberg *et al.*, 1987). It is thought that repeated exposure to regular physical activity and the resulting multiple episodes of lower blood pressure (BP) may translate into permanently lower BP. Similarly, BP reactivity to stress is blunted following an acute bout of exercise (Boone *et al.*, 1993; Ebbesen *et al.*, 1992; Probst *et al.*, 1997; Rejeski *et al.*, 1991; Rejeski *et al.*, 1992; Roy & Steptoe, 1991; Steptoe *et al.*, 1993; West *et al.*, 1998). Thus, the stress reactivity lowering mechanisms of acute exercise may play a more important role than that of long term chronic training adaptations.

The effect of acute exercise on cardiovascular reactivity to stress in offspring hypertensives has not been investigated before. Also, the effect of acute exercise on FBF reactivity to stress does not appear to have been studied at all. Therefore, the purpose of Study III was to investigate the effect of acute exercise on cardiovascular and FBF reactivity to mental challenge in males with a family history of hypertension. Based on the findings of Studies I and II it was hypothesised that acute exercise would reduce the cardiovascular and FBF response to mental challenge.

6.1 Protocol

Twelve healthy normotensive males with a family history of hypertension were recruited from a student population. The study was approved by a University human ethics committee and all subjects were provided written informed consent before participation. A within subjects study design was employed, where subjects acted as their own controls. The protocol was split into three separate days (see Appendix IIIB for a detailed protocol). The first day consisted of medical screening, explanation of the protocol, and a maximal oxygen uptake test (see Chapter 3). The second day consisted of either the exercise-stroop condition or control-Stroop condition. The third and final day consisted of the remaining condition depending on which one had been selected for day two. The order of days two and three for the exercise-Stroop condition or control-Stroop condition was counterbalanced between subjects. That is, subjects were randomly assigned to either the exercise-Stroop condition on day two and the control-Stroop condition on day three or the control-Stroop condition on day two and the exercise-Stroop condition on day three.

6.1.1 Medical Screening and Maximal Oxygen Uptake

Subjects were required to complete a full medical questionnaire and physical activity readiness questionnaire (Appendix IC, ID). Subjects were then provided with details on dietary guidelines (Appendix IIB) and information on the experimental protocol (Appendix IIIA). A maximal oxygen uptake ($\dot{V}O_{2max}$) test was then performed on a cycle ergometer (previously described in Chapter 3).

6.1.2 General Protocol

Subjects were required to follow dietary guidelines 24 hr prior to the second and third sessions, which included abstaining from alcohol and caffeine. Dietary guidelines were employed mainly to control for salt intake as this is known to effect

the cardiovascular stress reactivity response (Miller *et al.*, 1995) and may have provided a confounding variable. Subjects were also instructed to abstain from rigorous physical activity 24 hr before testing. Both sessions were performed in the morning after an overnight fast.

The basic protocol consisted of two stages for each condition; either an acute bout of cycle ergometry exercise followed by a 10-min Stroop mental challenge (exercise-Stroop condition) or a control period followed by a 10-min Stroop mental challenge (control-Stroop condition).

6.1.3. Exercise Session

The exercise session was performed on a stationary electronic ergometer (Excalibur Sport) in an air-conditioned laboratory held at constant room temperature of 19°C. To begin with subjects were instructed to perform a 5-min warm-up at a workload of 80 W and pedal cadence of 70-80 $rev.min^{-1}$. At the end of the warm-up period the load was adjusted to 60% of the subject's maximum workload that was designed to bring about an exercise intensity of 60-70% $\dot{V}O_{2max}$. Subjects were then required to cycle for 20 min at this intensity. HR was continuously monitored using a Polar heart rate monitor and gases were collected intermittently, every 5 min, using Douglas bags and later analysed for oxygen uptake. Rating of perceived exertion (Borg, 1962) was also attained every 5 min. If necessary, the load was adjusted in order to maintain an exercise intensity of 70-80% of heart rate reserve (calculated from the Karvonen formula). Afterwards, subjects were instructed to perform a 5-min cool-down period at a workload of 50 W and pedal cadence of 70-80 $rev.min^{-1}$.

6.1.4 Control Session

The control session was conducted in the same laboratory as the exercise session and consisted of body composition and dietary analysis for the duration of 30

min. Skin folds were measured from four sites using callipers, and body fat calculated from the Durnin and Wormsley (1974) formula. With the subject present, analysis was then performed on their dietary intake from the previous 24 hr using the computer software package *COMP-EAT* (Benson, 1989).

6.1.5 Stroop Mental Challenge

After the exercise or control session subjects were transferred to a separate laboratory that was quiet and air-conditioned, held at a constant room temperature of 24°C. Firstly, subjects were required to complete the STAI and then requested to lie down on a bed in the supine position. Subjects then rested quietly for approximately 25 min whilst they were prepared for the collection of data. An 8-min baseline period of data collection was then initiated. This consisted of 3 min of normal breathing and 3 min of paced breathing (10 cycles.min^{-1}). During minutes 6-8 baseline FBF was measured. After the baseline period the 10-min Stroop word/colour task (Stroop, 1935), described in the Chapter 3, was started. Subjects' perceived difficulty of the task, using the Borg 6-20 scale (Borg, 1962), together with mistakes were recorded. Subjects were encouraged to make as few mistakes as possible. FBF was measured during minutes 0-2 and 9-10 of the mental challenge, but all other cardiovascular variables were measured continuously. Five minutes of recovery in the supine position followed the mental challenge, during which FBF was measured for the first 2 min but all other variables were measured continuously.

6.2 Statistical Analysis

A 2 × 5 repeated measures analysis of variance (ANOVA) was employed to identify changes in cardiovascular variables over time and condition. The within subject factor comprised of baseline, minutes 0-2, 5-6, and 9-10 of Stroop, and recovery. The between subject factor was the two conditions (exercise and control). A

2×4 repeated measures ANOVA was employed to identify changes in FBF, forearm vascular resistance (FVR), and forearm vascular conductance (FVC) that comprised of four within subject factors (baseline, minutes 0-2 and 9-10 of Stroop, and recovery). Bonferonni post-hoc analysis was performed where required and statistical significance was assumed at a value of $P<0.05$.

6.3 Results

6.3.1 Subject Characteristics, Dietary Intake, and Exercise Details

Physical characteristics of subjects and dietary intake details are displayed in Table 6.1. All subjects were moderately active displaying above average levels of physical fitness and were in the normal range for body fat values.

All subjects completed the sub-maximal exercise protocol that was performed at a workload of (mean ± *SEM*; 199 ± 7.7 W), corresponding to an exercise intensity of 67.3 ± 3.5% $\dot{V}O_{2max}$, a heart rate reserve of 81.5 ± 1.8%, and a mean heart rate of 168 ± 3.5 $b.min^{-1}$. The exercise was perceived as "hard" on the Borg 6-20 scale (15.7 ± 0.4) and subjects demonstrated post-exercise reductions in body mass (0.18 ± 0.05 kg).

All subjects reported a history of hypertension that was apparent in first-degree relatives. Five subjects reported a single hypertensive parent, whilst two subjects reported a biparental history of hypertension. The remainder of the subjects reported family history of hypertension that was apparent in their grandparents.

Table 6.1. Descriptive characteristics and 24 hour dietary intake (mean ± *SEM*).

Variable	
Age (years)	19.2 ± 0.4
Body mass (kg)	78.6 ± 2.6
Height (cm)	180.5 ± 1.2
Body fat %	16.7 ± 1.0
$\dot{V}O_{2max}$ ($ml.kg^{-1}.min^{-1}$)	41.6 ± 2.6
Calorie consumption (kcal)	1863 ± 118
Total salt intake (g)	7.8 ± 0.7

6.3.2 Psychological Responses

There were no significant differences in state anxiety (35.0 ± 2.2 versus 30.0 ± 1.9) between exercise and control days respectively. During the Stroop mental challenge there was no significant differences in perceived task difficulty (13.3 ± 0.4 versus 13.6 ± 0.7) or mistakes (44.8 ± 9.5 versus 60.0 ± 13.4) between exercise and control conditions respectively.

6.3.3 Cardiovascular Responses

6.3.3.1 Central cardiovascular responses. For heart rate (HR) there was a significant main effect [F (4, 88) = 79.3, P<0.05], and effect between conditions [F (1, 22) = 15.68, P<0.05]. HR was significantly increased throughout Stroop in comparison with baseline. Subjects displayed a significantly elevated post-exercise HR at baseline, Stroop, and recovery in comparison with control conditions. When comparing HR change scores there was a significant effect between conditions [F (1, 22) = 6.5, P<0.05]. Subsequent analysis revealed significantly lower post-exercise change scores at minutes 5-6 and 9-10 of the Stroop, and during recovery, with respect to baseline, and in comparison with control (see Figure 6.1a and Table 6.2).

There were no significant effects for cardiac output (CO) (see Figure 6.1b and Table 6.2) although there was a trend for an elevated post-exercise CO at baseline.

There was a significant main effect for stroke volume (SV) [F (4, 88) = 37.1, P<0.05], but no interaction or between subject effects. SV was significantly reduced during Stroop and there was a trend for lower post-exercise SV at baseline and throughout (see Figure 6.1c and Table 6.2).

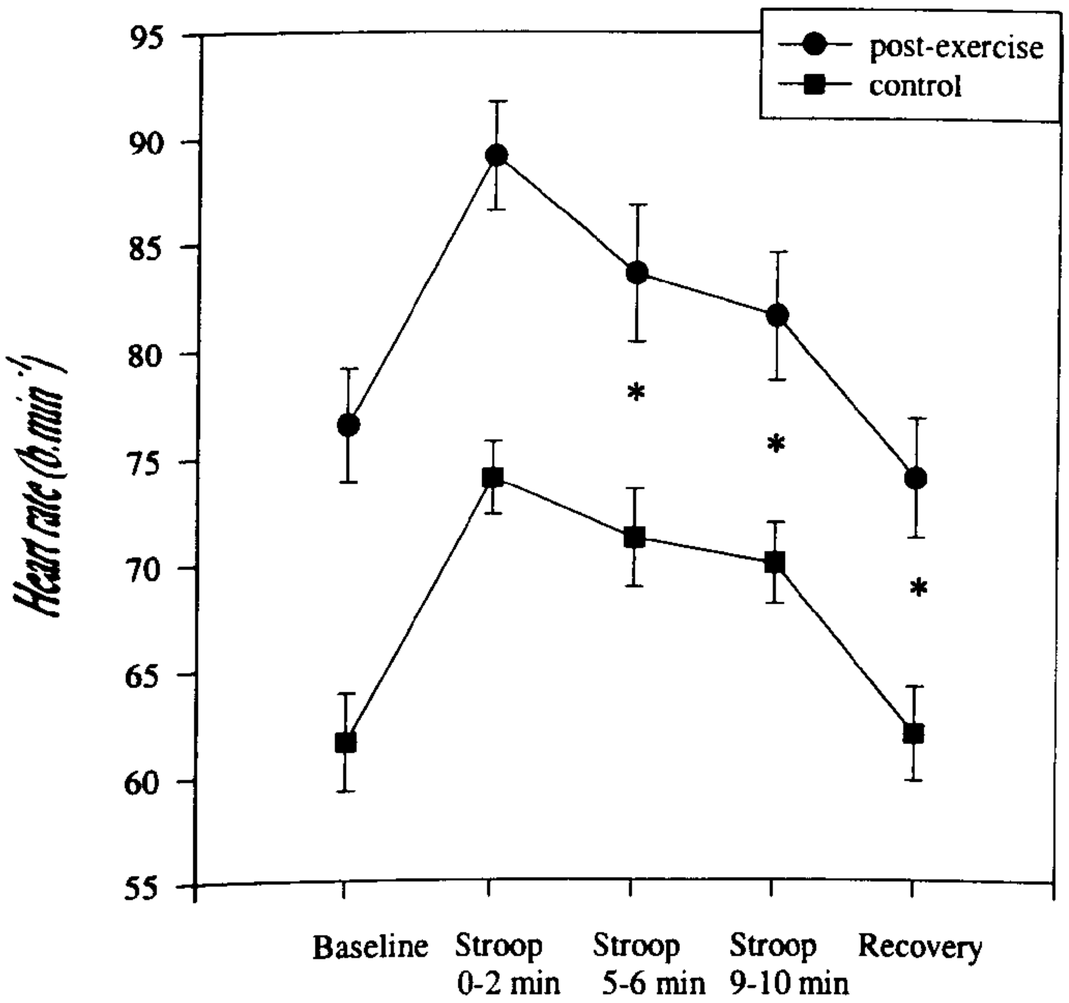


Figure 6.1a. The effect of acute exercise on heart rate response during Stroop.

* Significantly different change score in comparison with baseline, between conditions.

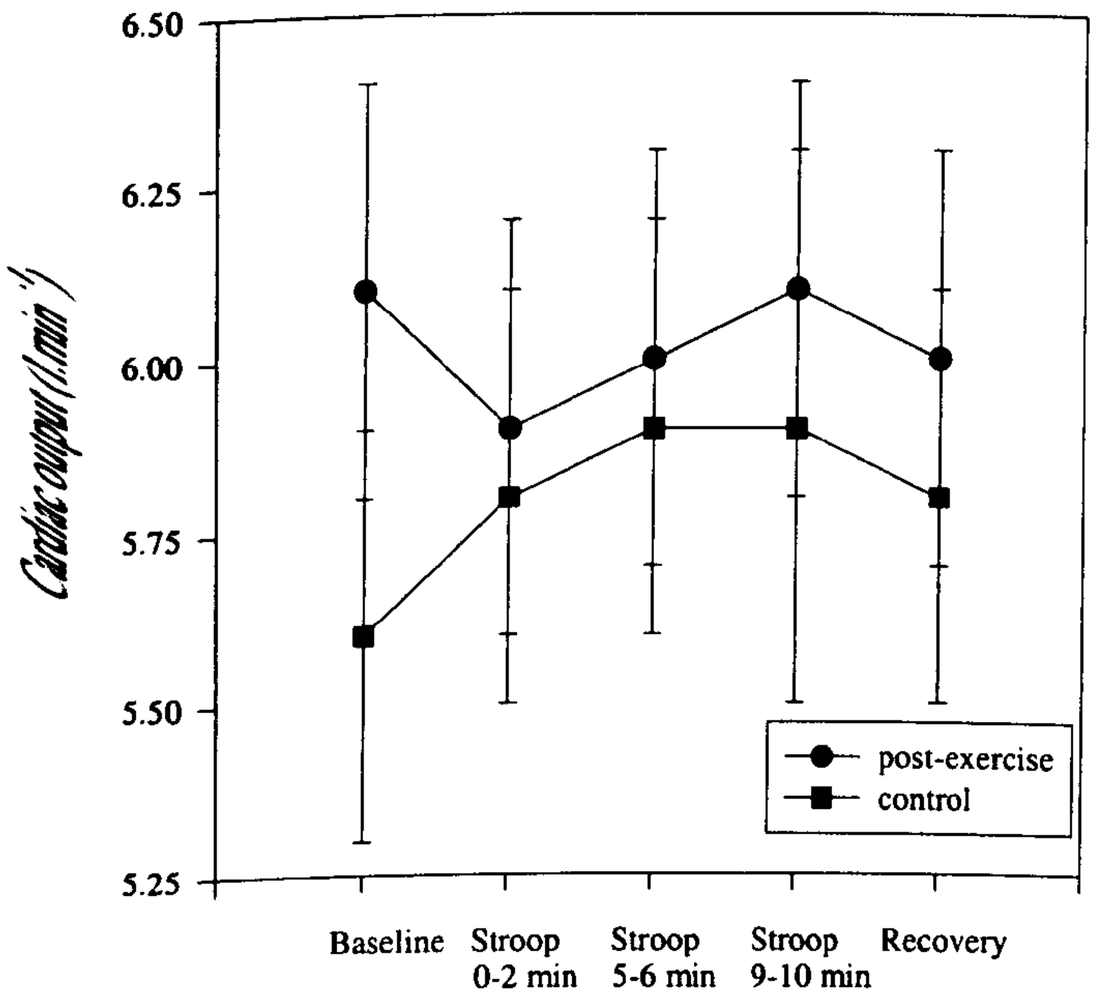


Figure 6.1b. The effect of acute exercise on cardiac output response during Stroop.

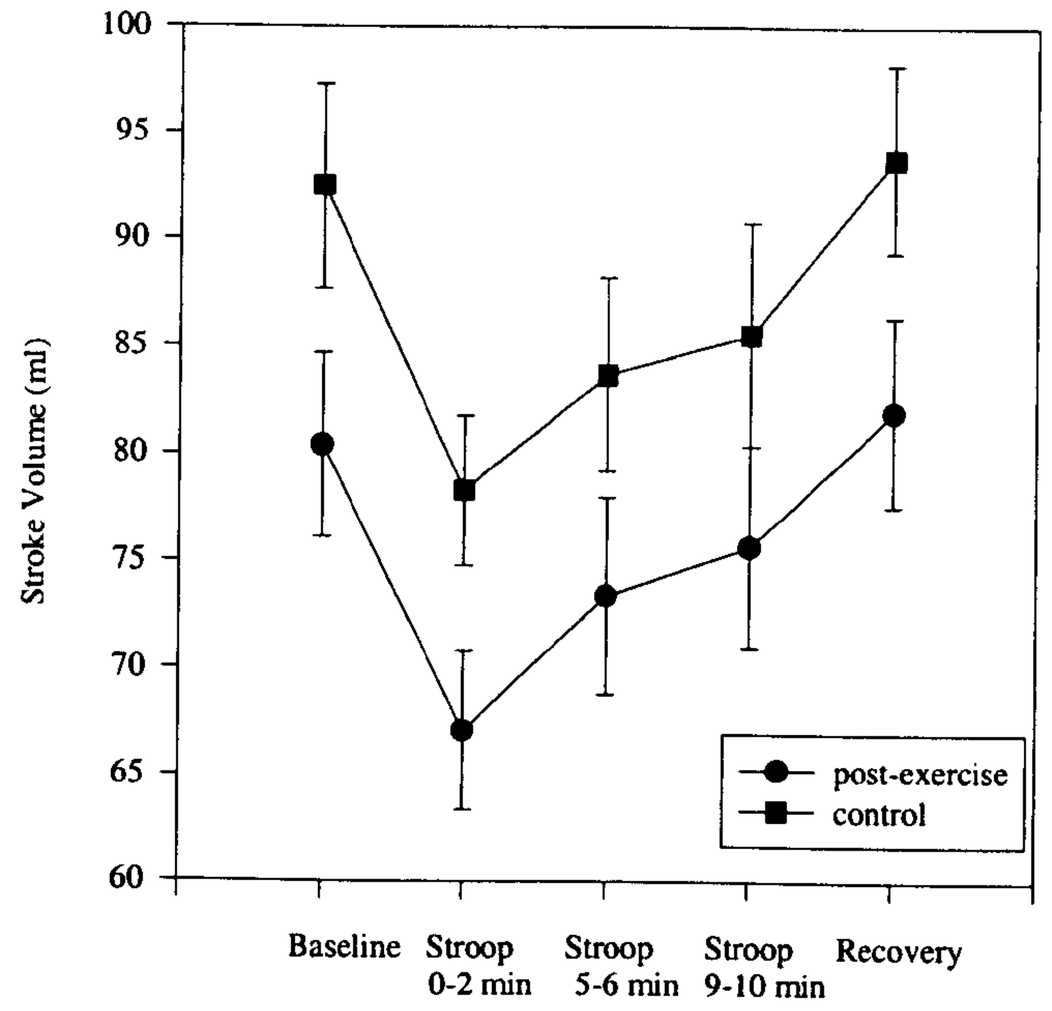
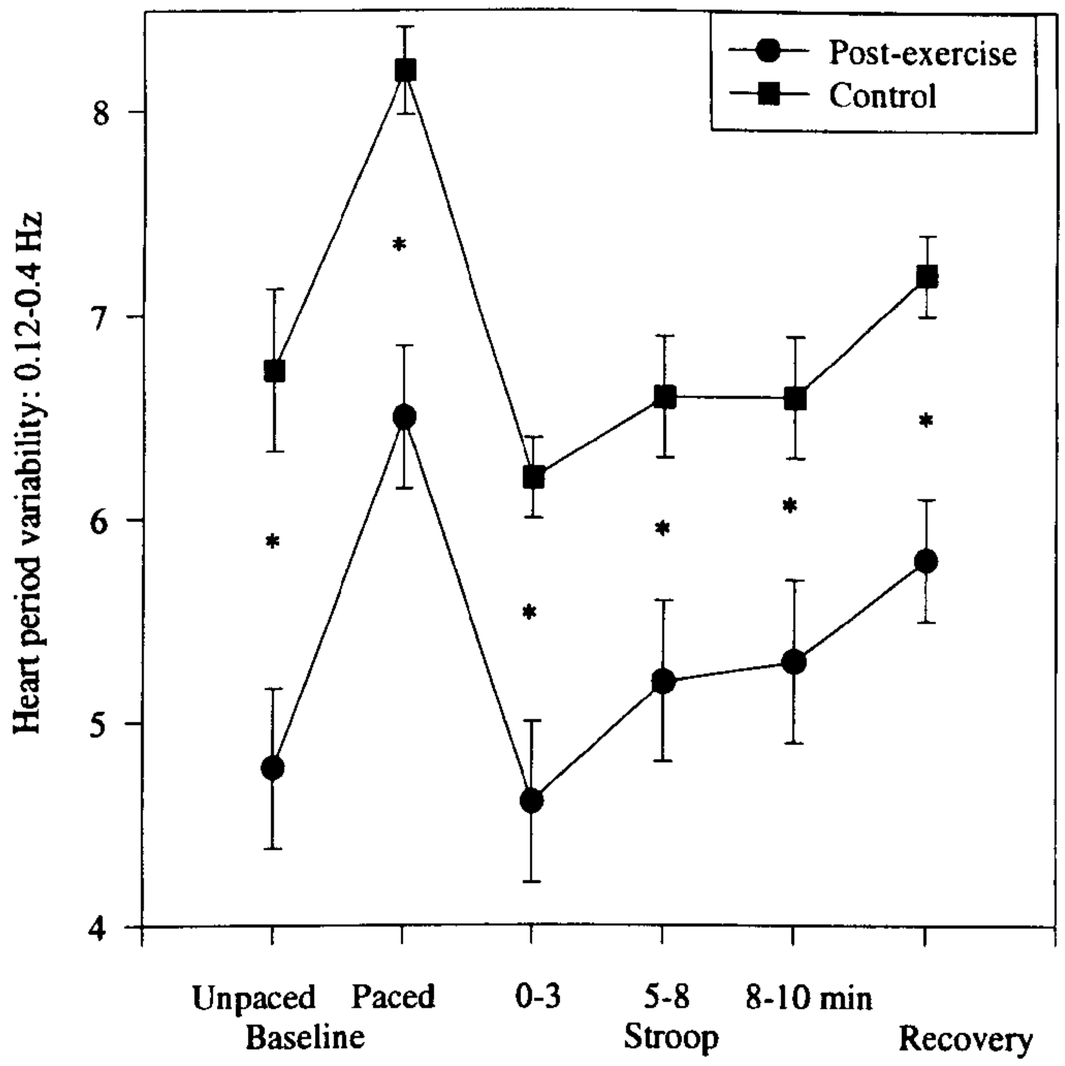


Figure 6.1c. The effect of acute exercise on stroke volume response during Stroop.

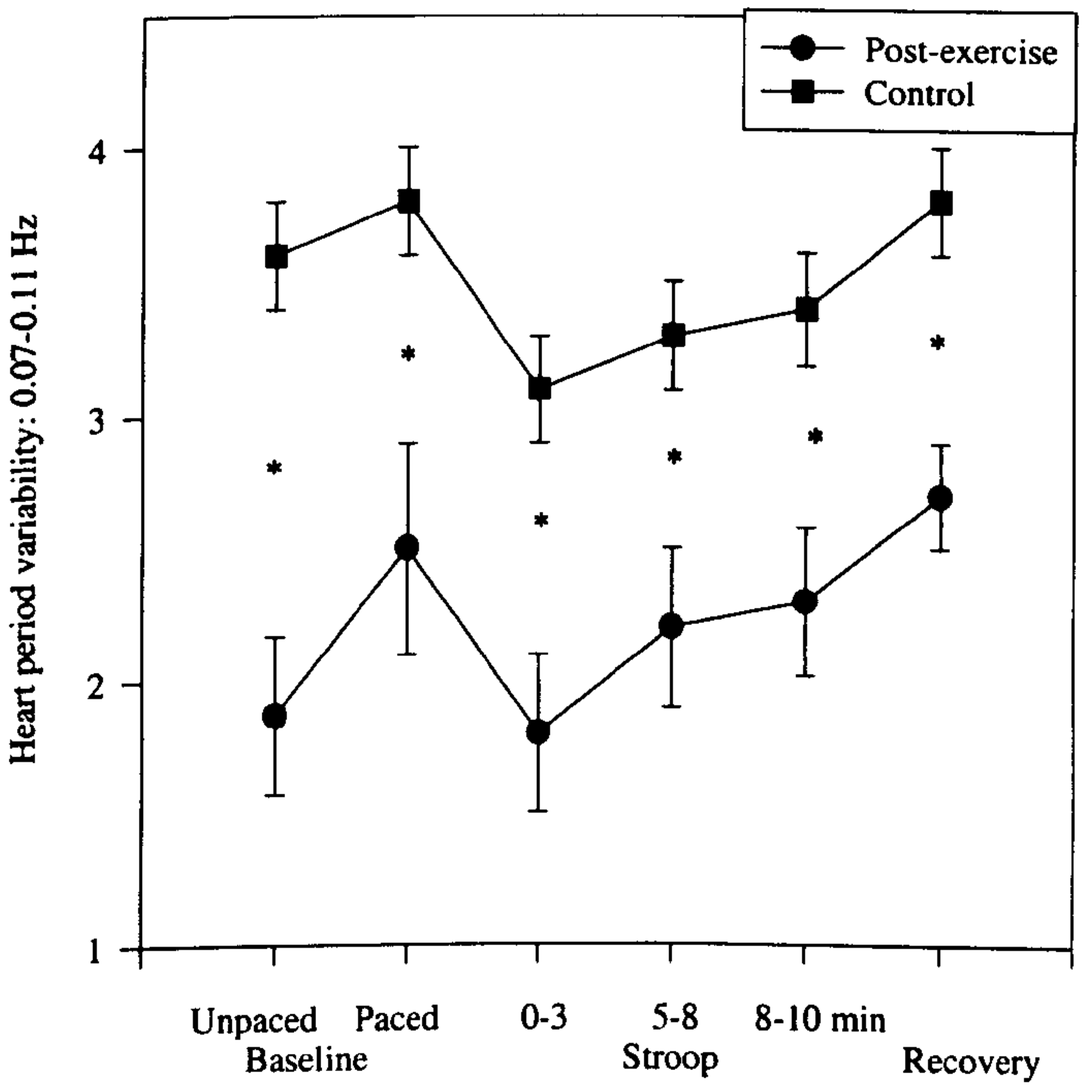
6.3.3.2 Cardiac autonomic responses. There was a significant main effect within subjects for time series analysis of heart period variability (HPV_{ts}) in the high frequency domain (0.12-0.4 Hz) [F (4, 88) = 9.47, P<0.05] and an effect between conditions [F (1, 22) = 12.68, P<0.05]. HPV_{ts} was significantly reduced during Stroop and recovery across time in comparison with baseline (paced breathing). Also there was a significant reduction in post-exercise HPV_{ts} in comparison with control, which reflected the significantly elevated post-exercise HR (see Figure 6.2a and Table 6.2).

There was a significant effect between conditions [F (1, 22) = 13.49, P<0.05] for HPV_{ts} in the medium frequency domain (0.07-0.11 Hz). HPV_{ts} in the medium frequency domain was significantly blunted post-exercise in comparison with control (see Figure 6.2b and Table 6.2).



* Significant difference between conditions ($P<0.05$)

Figure 6.2a. The effect of acute exercise on heart period variability at high frequencies during Stroop.



* Significant difference between conditions ($P<0.05$)

Figure 6.2b. The effect of acute exercise on heart period variability at medium frequencies during Stroop.

6.3.3.3 Cardiac contractility. There was a significant main effect over time for pre-ejection period (PEP) [F (4, 88) = 3.38, P<0.05] but no effects between condition. PEP was significantly reduced during Stroop with respect to baseline. There were no differences in change scores between conditions (see Figure 6.3a and Table 6.2).

There was a significant main time effect [F (4, 88) = 48.2, P<0.05] and effect between conditions [F (1, 22) = 5.95, P<0.05] for left ventricular ejection time (LVET). LVET was significantly reduced during Stroop with respect to baseline. Also, post-exercise LVET was significantly lower across time compared with control reflecting an elevated post-exercise HR. There were no significant differences in change scores between conditions (see Figure 6.3b and Table 6.2).

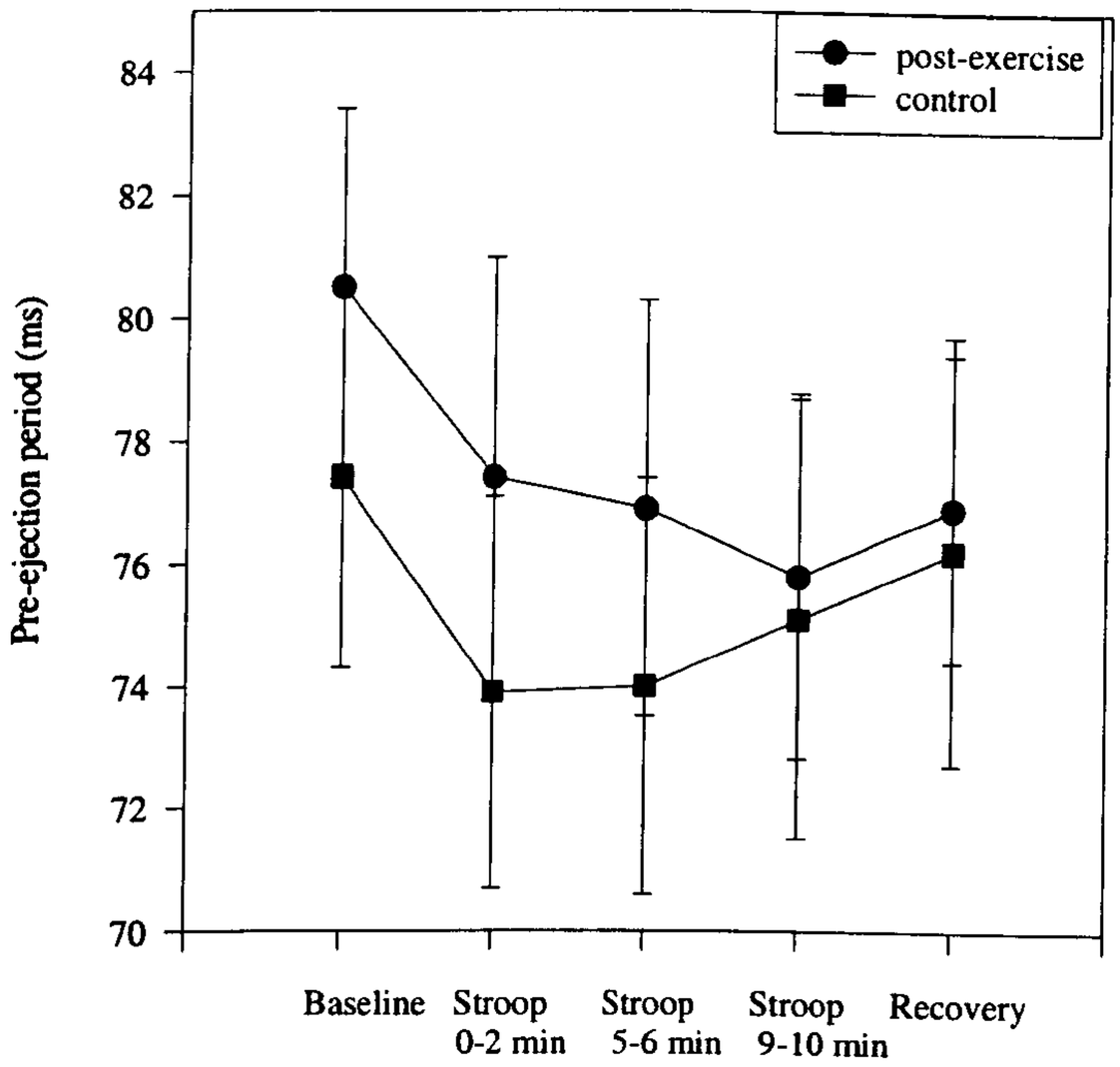


Figure 6.3a. The effect of acute exercise on pre-ejection period response during Stroop.

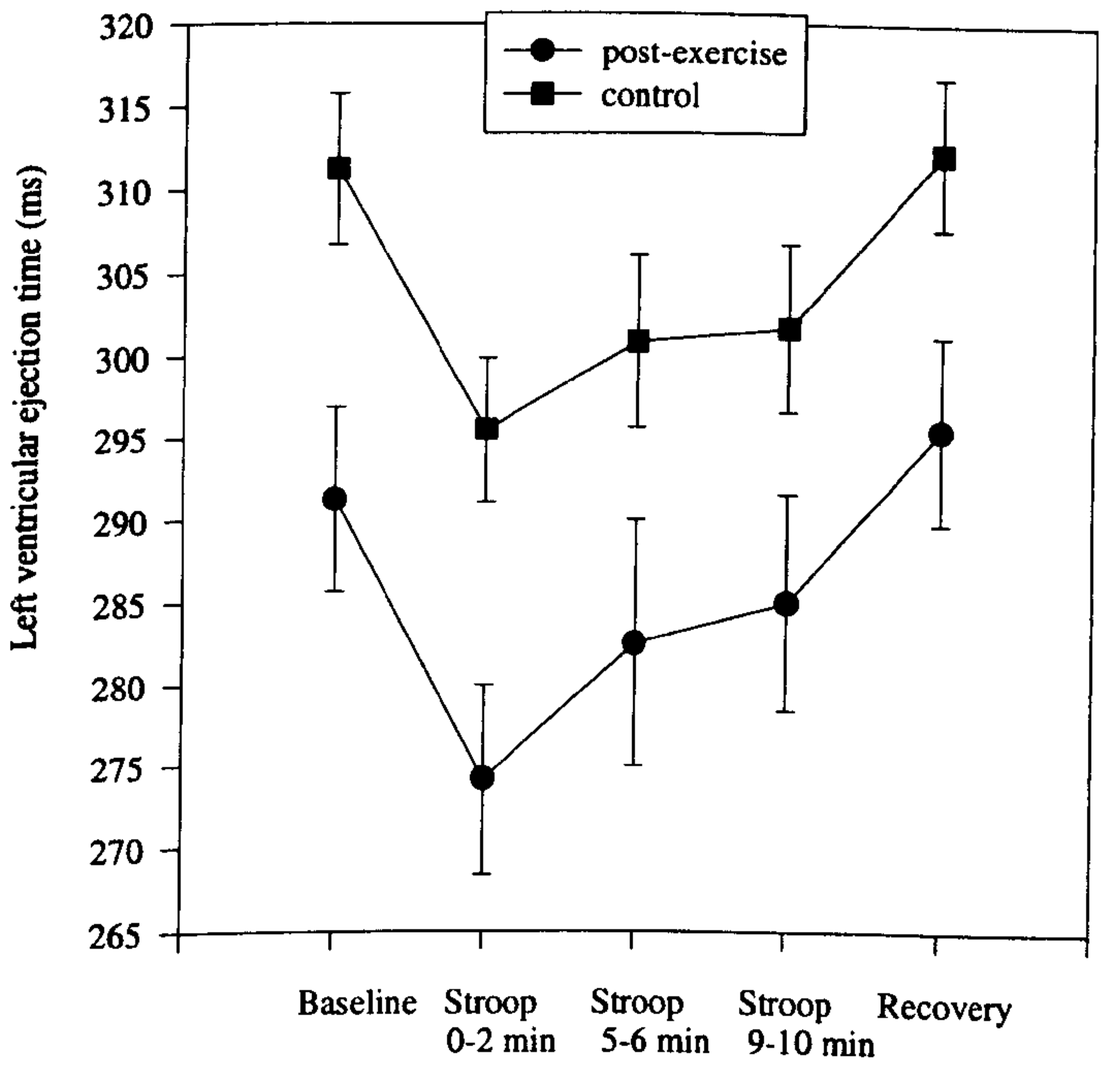
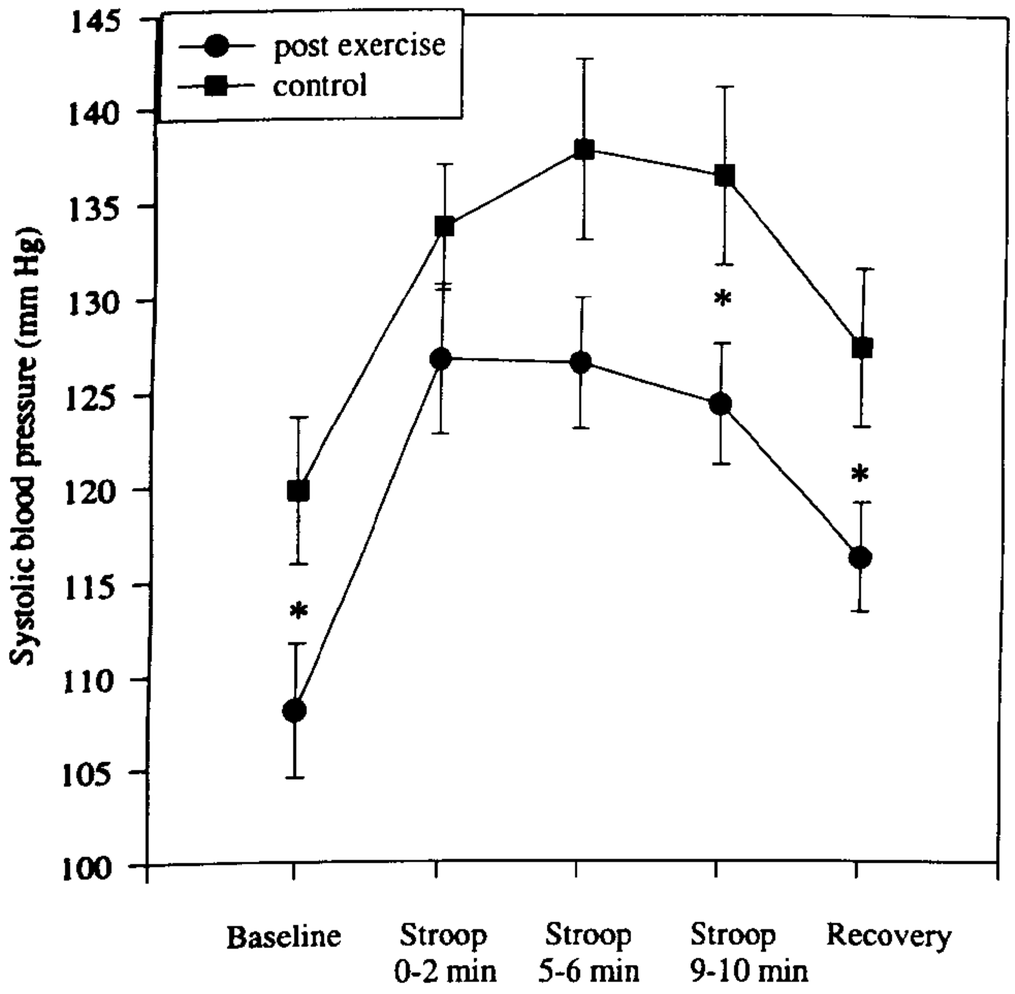


Figure 6.3b. The effect of acute exercise on left ventricular ejection time response during Stroop.

6.3.3.4 Blood pressure and rate pressure product responses. There was a significant main effect across time for systolic blood pressure (SBP) [F (4, 88) = 38.8, P<0.05], diastolic blood pressure (DBP) [F (4, 88) = 67.35, P<0.05], and mean arterial pressure (MAP) [F (4, 88) = 61.9, P<0.05]. SBP, DBP, and MAP were significantly increased during Stroop and recovery with respect to baseline. There was a significant effect between conditions for SBP [F (1, 22) = 4.49, P<0.05] and further analysis showed that post-exercise SBP was significantly reduced at baseline [F (1, 22) = 4.78, P<0.05, ES = 0.9], Stroop (9-10 min) [F (1, 22) = 4.5, P<0.05, ES = 0.9], and recovery [F (1, 22) = 4.6, P<0.05, ES = 0.9] in comparison with control. For DBP and MAP there was a trend for a post-exercise hypotensive effect.

There was a significant main effect across time for rate pressure product (RPP) [F (4, 88) = 78.7, P<0.05]. RPP, which is an indicant of myocardial oxygen consumption, was significantly increased during Stroop and recovery with respect to baseline. There were no significant differences between condition (see Figures 6.4a, b, c, d and Table 6.2).



* significant difference between conditions ($P<0.05$)

Figure 6.4a. The effect of acute exercise on systolic blood pressure response during Stroop.

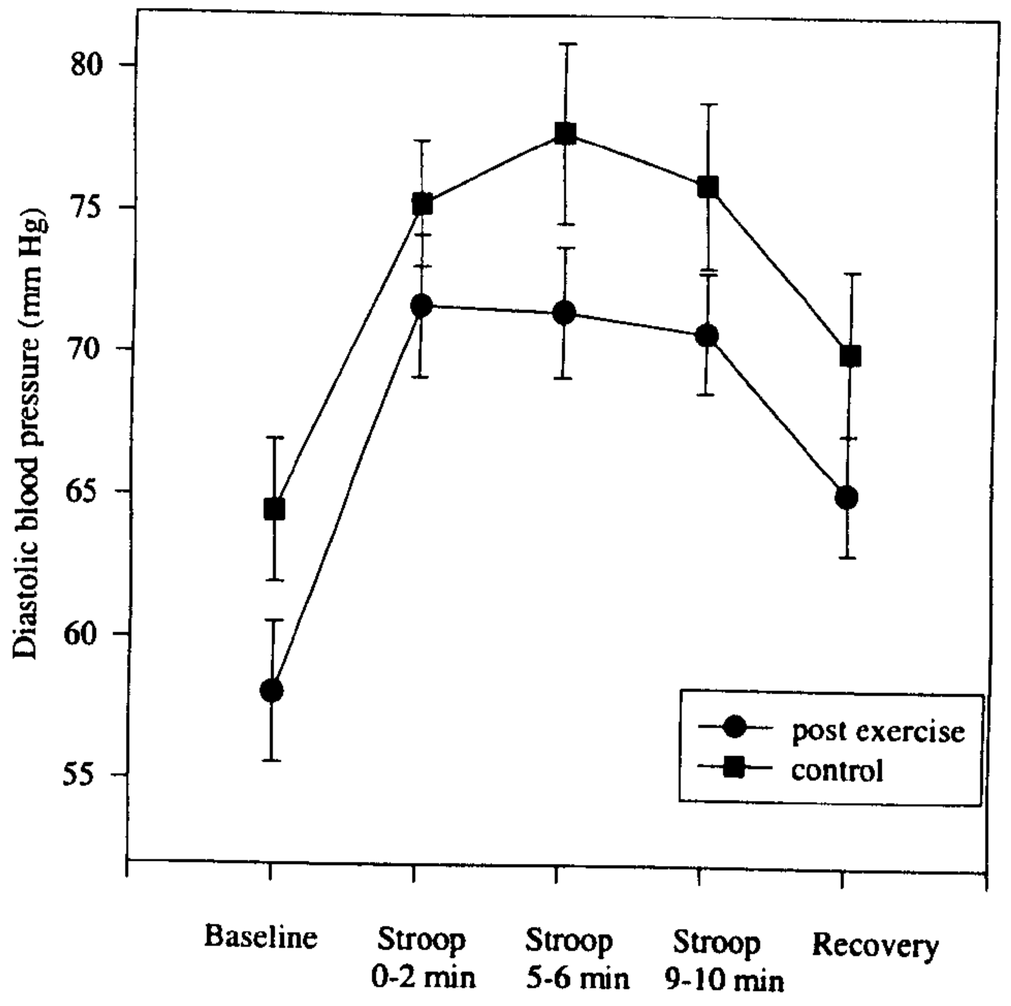


Figure 6.4b. The effect of acute exercise on diastolic blood pressure response during Stroop.

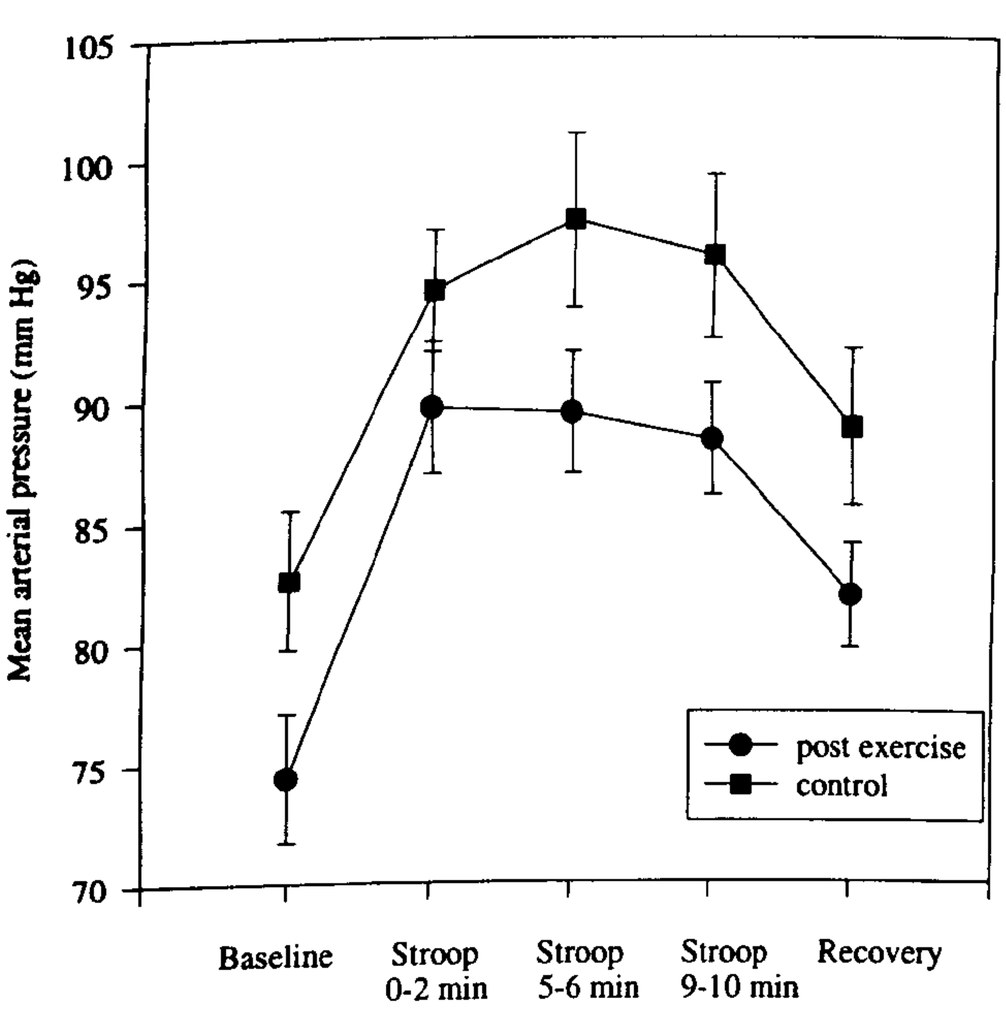


Figure 6.4c. The effect of acute exercise on mean arterial pressure response during Stroop.

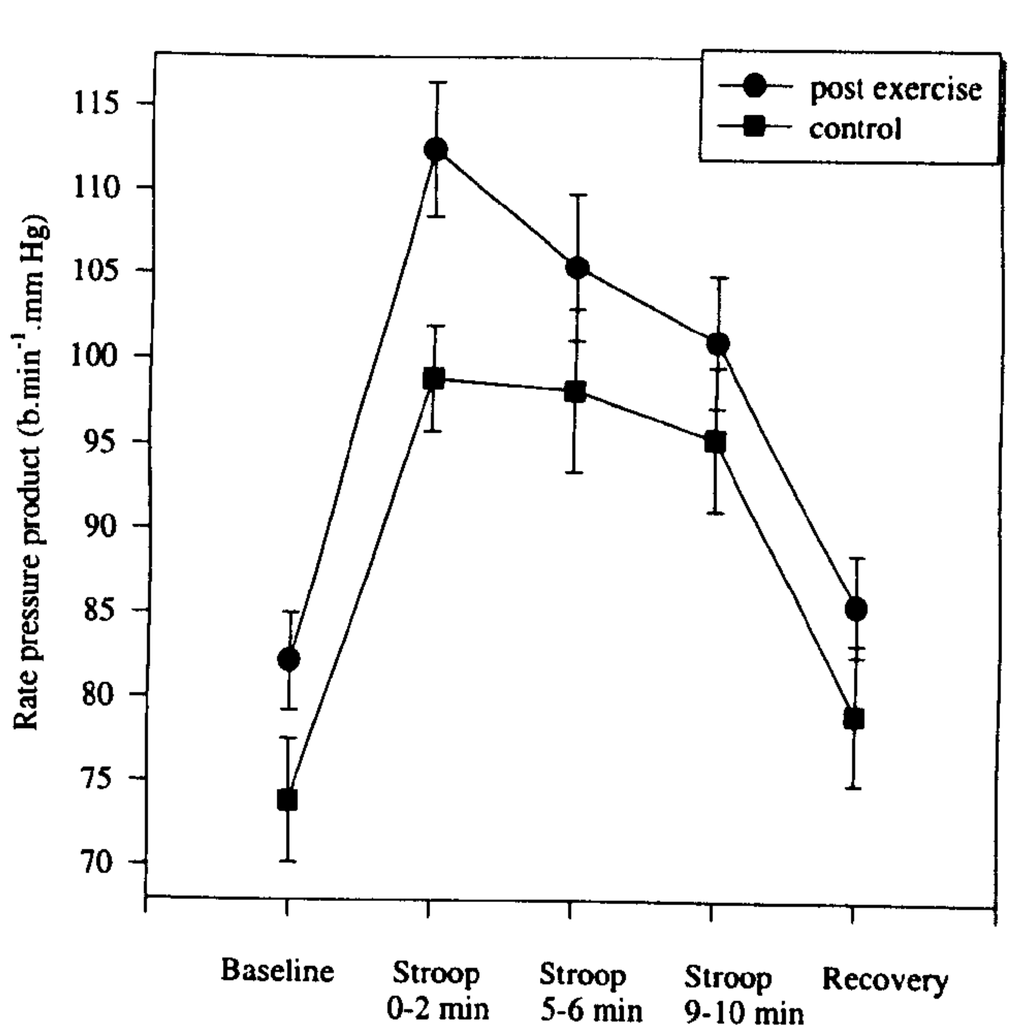


Figure 6.4d. The effect of acute exercise on rate pressure product response during Stroop.

3.3.2 Cardiovascular Measures

3.3.2.1 The electrocardiogram (ECG). A three lead ECG was recorded using an Amlab physiograph (Model 1.7) system, which was linked to a 386 PC computer. R-R interval was recorded at a sampling rate of 1000 Hz.

3.3.2.2 The impedance cardiogram (ICG). The impedance technique was employed to measure stroke volume (SV) and cardiac output (CO). ICG was recorded with a Minnesota impedance cardiograph (model 304B), from four silver tape band electrodes. Two of the bands were attached around the neck, a third around the thorax, and the fourth was placed around the abdomen between the xiphoid and umbilicus (see Figure 3.1). The two outer electrodes (electrode #1 cephalad, and electrode #4 caudal) were spaced at least 3 cm from the inner electrodes to avoid nonlinearities in the electrical field. A constant, sinusoidal ac current was applied through electrodes one and four, which establishes an electric field between the outer electrodes while the inner electrodes detect change in voltage with which to determine changes in impedance. The decrease in thoracic impedance, denoted by an up stroke of the impedance signal and thought to be generated by the ejection of blood from the heart has been quantitatively related to the volume of blood ejected. The impedance signal is composed of three components relevant to the determination of stroke volume; the largest is basal thoracic impedance and reflects the conductance of the total thoracic mass (tissues, fluid, and air). Respiratory activity induces approximately a 3% change in the thoracic impedance signal, whilst cardiac activity comprises less than 1% of the basic impedance signal. The differentiated impedance cardiogram (*dZ/dt* waveform – see Figure 3.2) was used to calculate SV using the formula proposed by Kubicek *et al.* (1966; 1970) shown below:-

6.3.3.5 Peripheral vascular responses. There was a significant main effect over time for total peripheral resistance (TPR) [F (4, 88) = 12.96, P<0.05]. TPR was significantly increased during Stroop and recovery with respect to baseline. Although there were no significant effects between condition there was a trend for post-exercise reductions in TPR across time in comparison with control (see Figure 6.5a and Table 6.2).

There was a significant main effect over time for FBF [F (3, 66) = 28.9, P<0.05]. FBF was significantly increased during Stroop and recovery with respect to baseline. When comparing FBF change scores there was a significant effect between conditions [F (1, 22) = 7.9, P<0.05]. Subsequent analysis revealed significantly lower post-exercise change scores during the Stroop, with respect to baseline, and in comparison with control. Thus suggesting lower FBF reactivity post-exercise (see Figures 6.5b, c and Table 6.2).

There was a significant main effect over time [F (3, 66) = 13.7, P<0.05], interaction [F (3, 66) = 7.6, P<0.05], and effect between condition [F (1, 22) = 8.7, P<0.05] for FVR. FVR was significantly decreased during Stroop and recovery with respect to baseline. Also, when comparing FVR change scores there was a significant effect between conditions [F (1, 22) = 7.9, P<0.05]. Subsequent analysis revealed significantly lower post-exercise change scores during the Stroop, with respect to baseline, and in comparison with control (see Figures 6.5d, e and Table 6.2).

Similarly, for FVC there was a significant main effect over time [F (3, 66) = 10.1, P<0.05] and effect between condition [F (1, 22) = 4.9, P<0.05]. FVC was significantly increased during Stroop and recovery with respect to baseline. Also, when comparing FVC change scores there was a significant effect between conditions [F (1, 22) = 9.7, P<0.05]. Subsequent analysis revealed significantly lower post-

exercise change scores during the Stroop, with respect to baseline, and in comparison with control (see Figures 6.5f, g and Table 6.2).

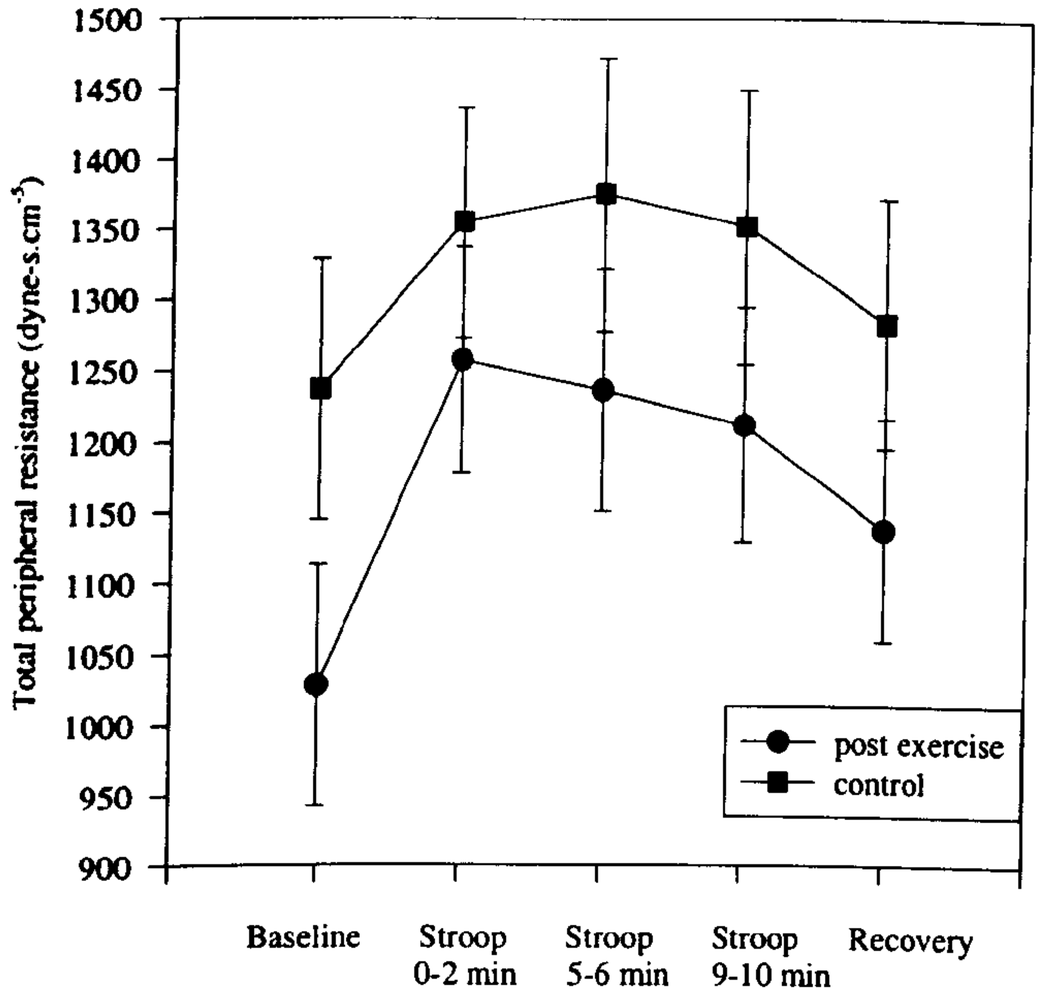
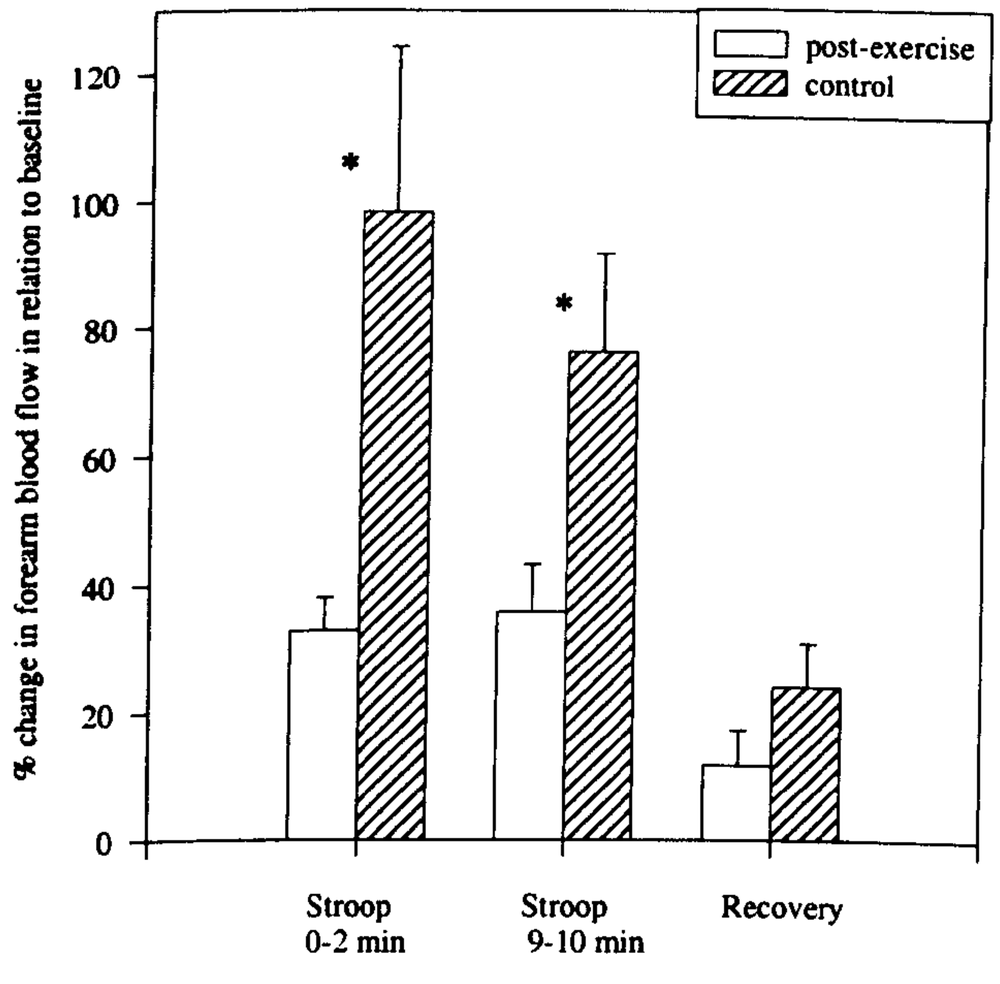


Figure 6.5a. The effect of acute exercise on total peripheral resistance response during Stroop.



* significant difference between conditions ($P<0.05$)

Figure 6.5b. The effect of acute exercise on forearm blood flow reactivity to Stroop mental challenge.

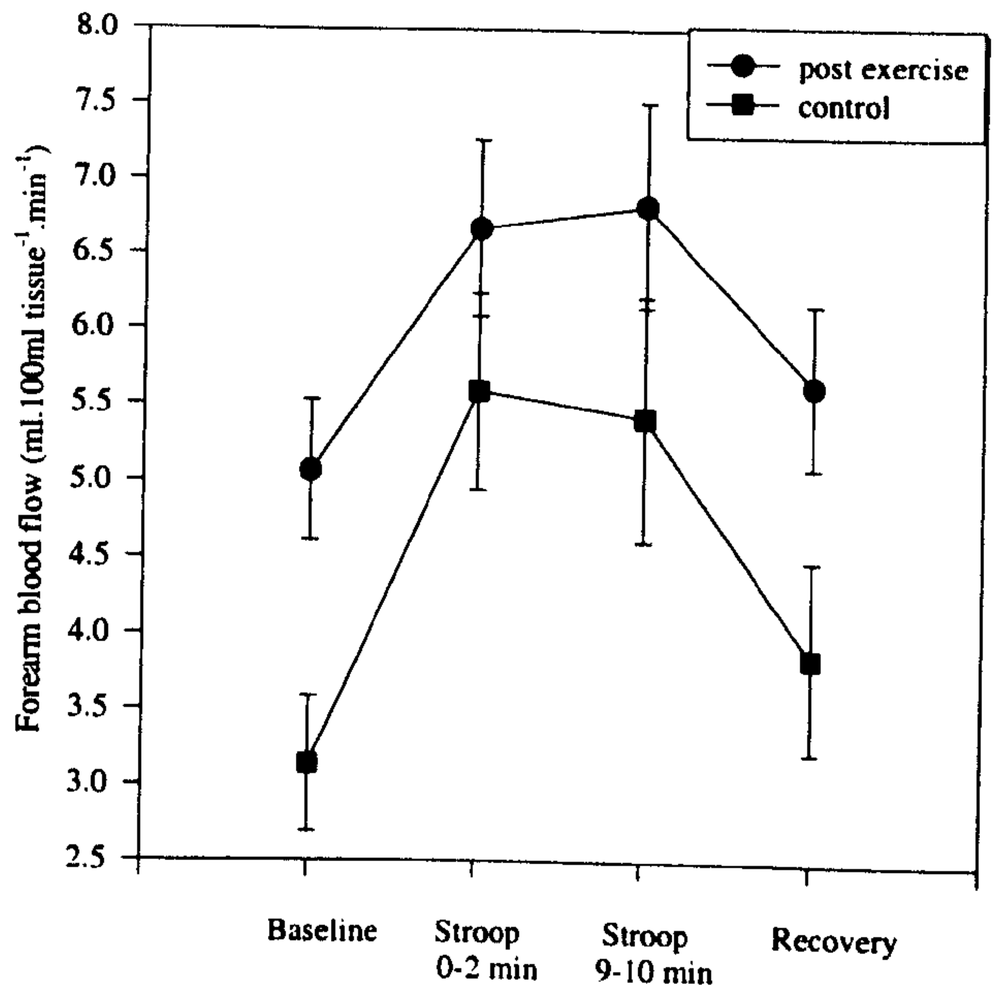
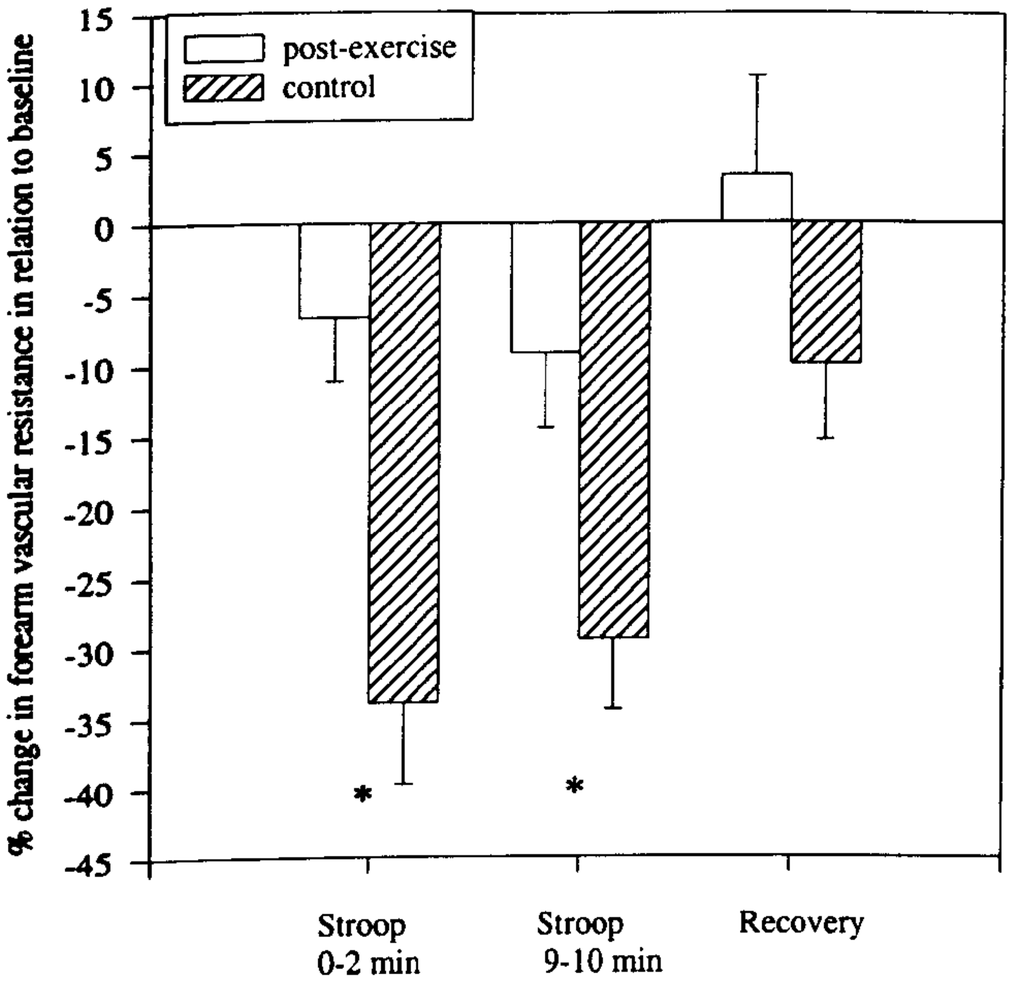
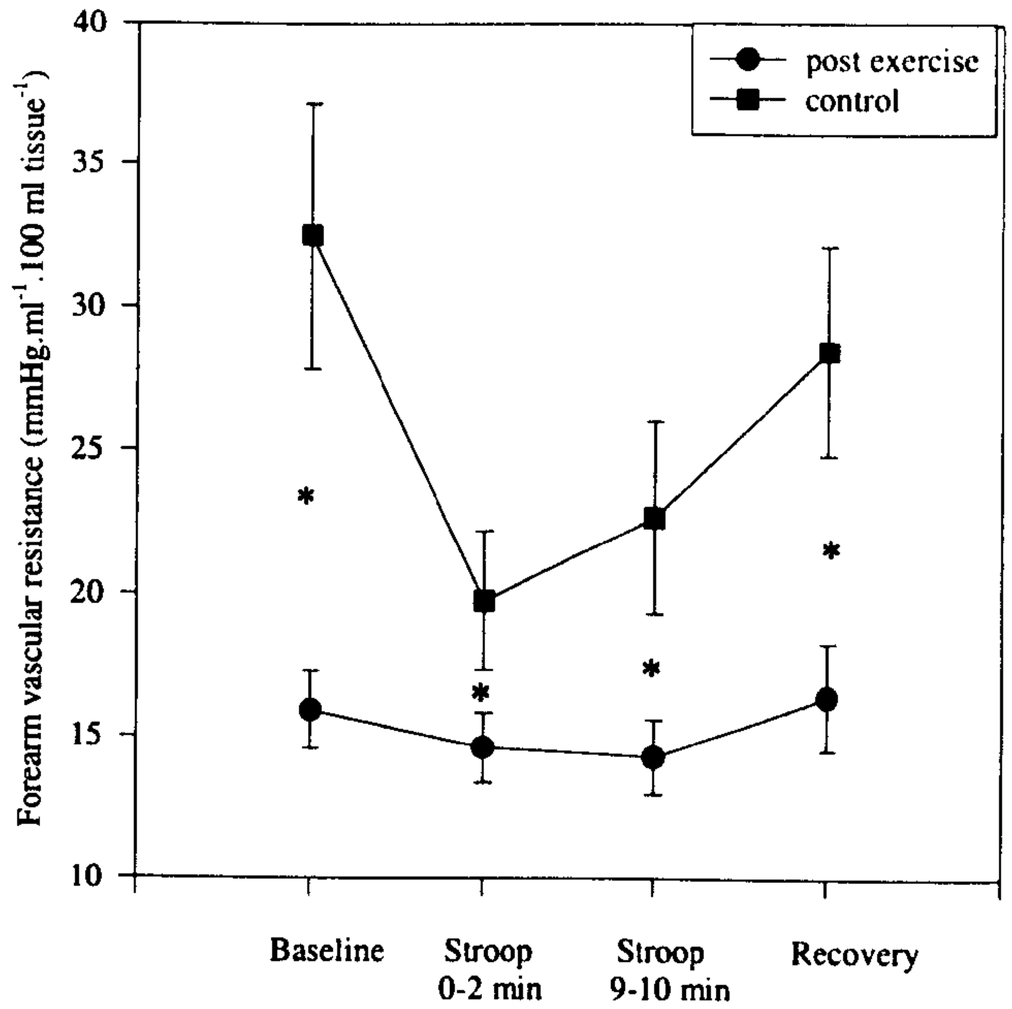


Figure 6.5c. The effect of acute exercise on forearm blood flow response to Stroop.



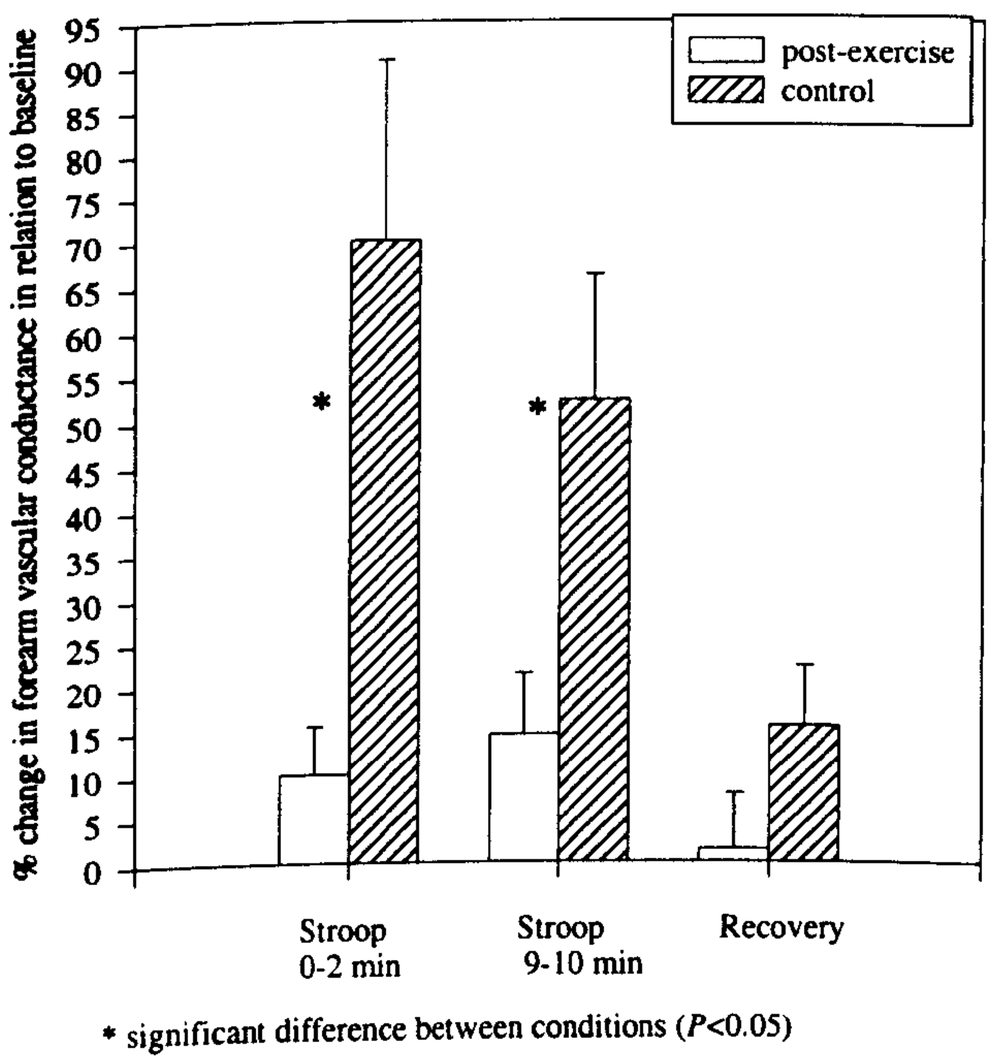
* significant difference between conditions ($P<0.05$)

Figure 6.5d. The effect of acute exercise on vascular reactivity to Stroop.



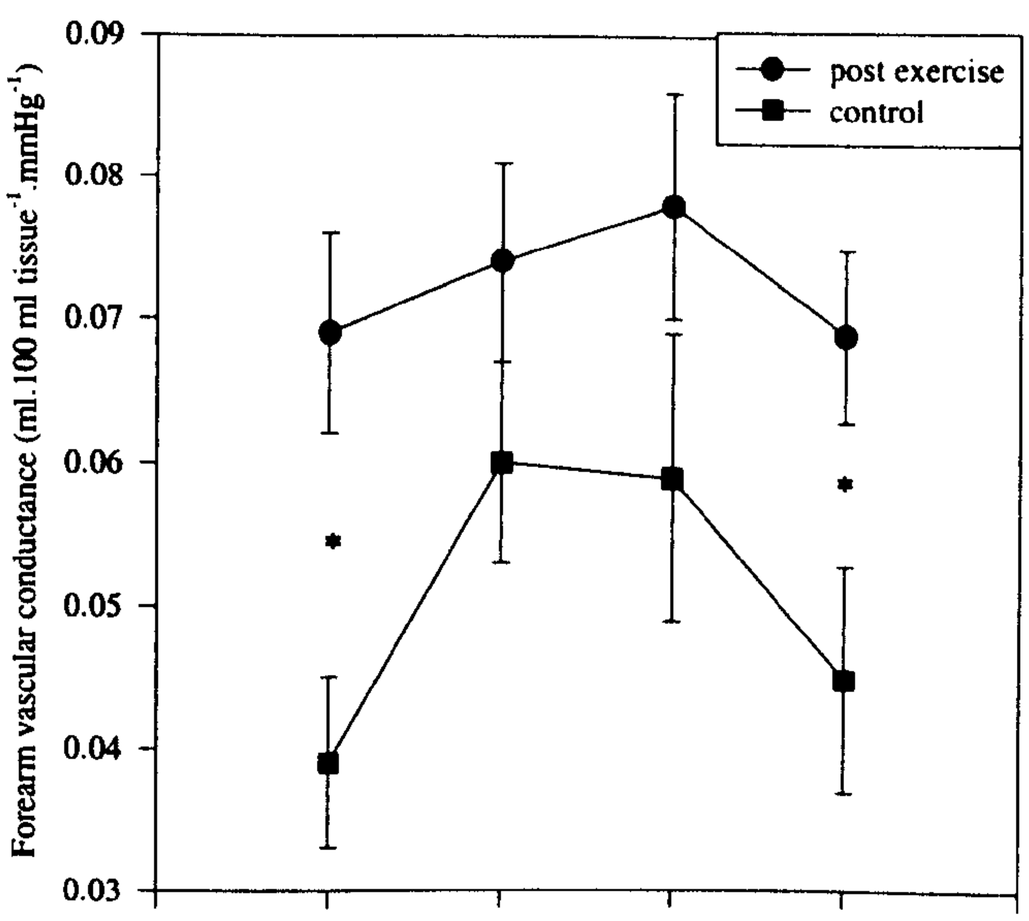
* significant difference between condition

Figure 6.5e. The effect of acute exercise on forearm vascular resistance response to Stroop.



* significant difference between conditions ($P<0.05$)

Figure 6.5f. The effect of acute exercise on vascular reactivity to Stroop mental challenge.



* significant difference between condition ($P<0.05$)

Figure 6.5g. The effect of acute exercise on forearm vascular conductance response to Stroop.

6.3.3.6. Pearson correlations. There was a significant correlation between post-exercise percentage change in FVR, in comparison with control, and control FVR (r = -0.72, P<0.05), indicating subjects with higher FVR on the control day demonstrated a greater percentage decrease in FVR post exercise. Similarly, for FVC, subjects with lower FVC on the control day demonstrated greater percentage increases in FVC post-exercise (r = -0.64, P<0.05) (see Figures 6.6a and b).

There was a significant correlation between post-exercise percentage change in FVR, in comparison with control, and exercise intensity (r = -0.80, P<0.05), indicating subjects who worked at a higher percentage of their $\dot{V}O_{2max}$ demonstrated a greater percentage decrease in FVR post exercise. Similarly, for FVC, subjects who worked at a higher percentage of their $\dot{V}O_{2max}$ demonstrated greater percentage increases in FVC post-exercise (r = 0.71, P<0.05) (see Figures 6.6c and d).

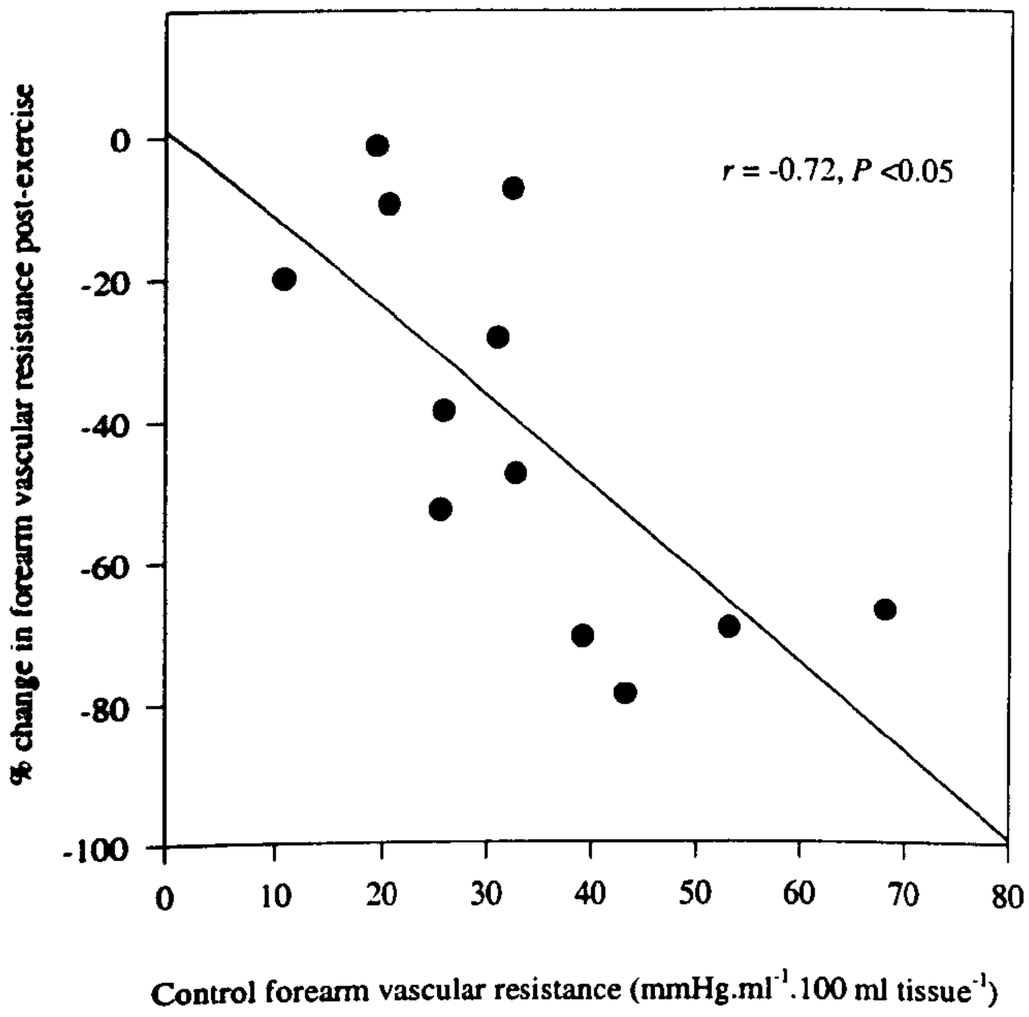


Figure 6.6a. Relationship between control forearm vascular and percentage change in forearm vascular resistance post exercise.

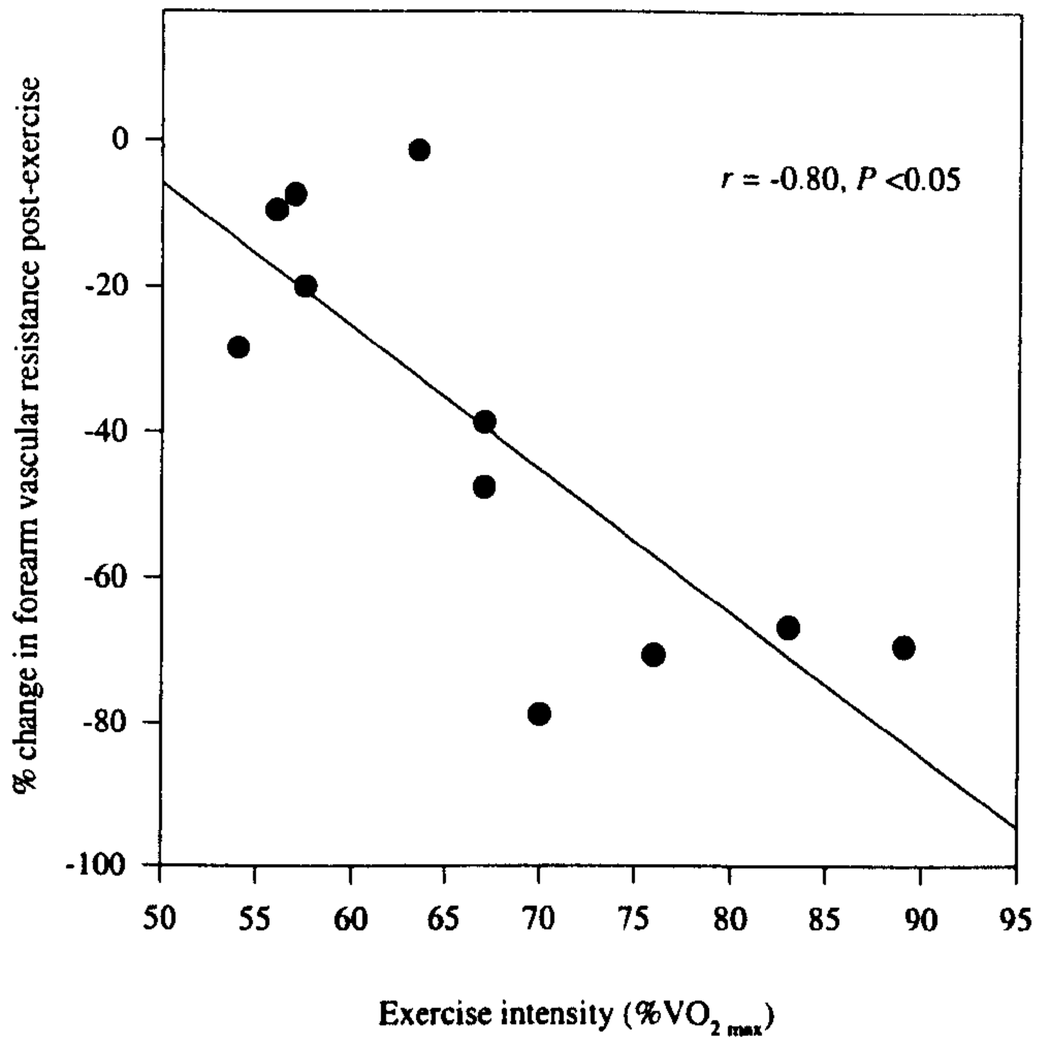


Figure 6.6c. Relationship between exercise intensity and percentage change in forearm vascular resistance post exercise.

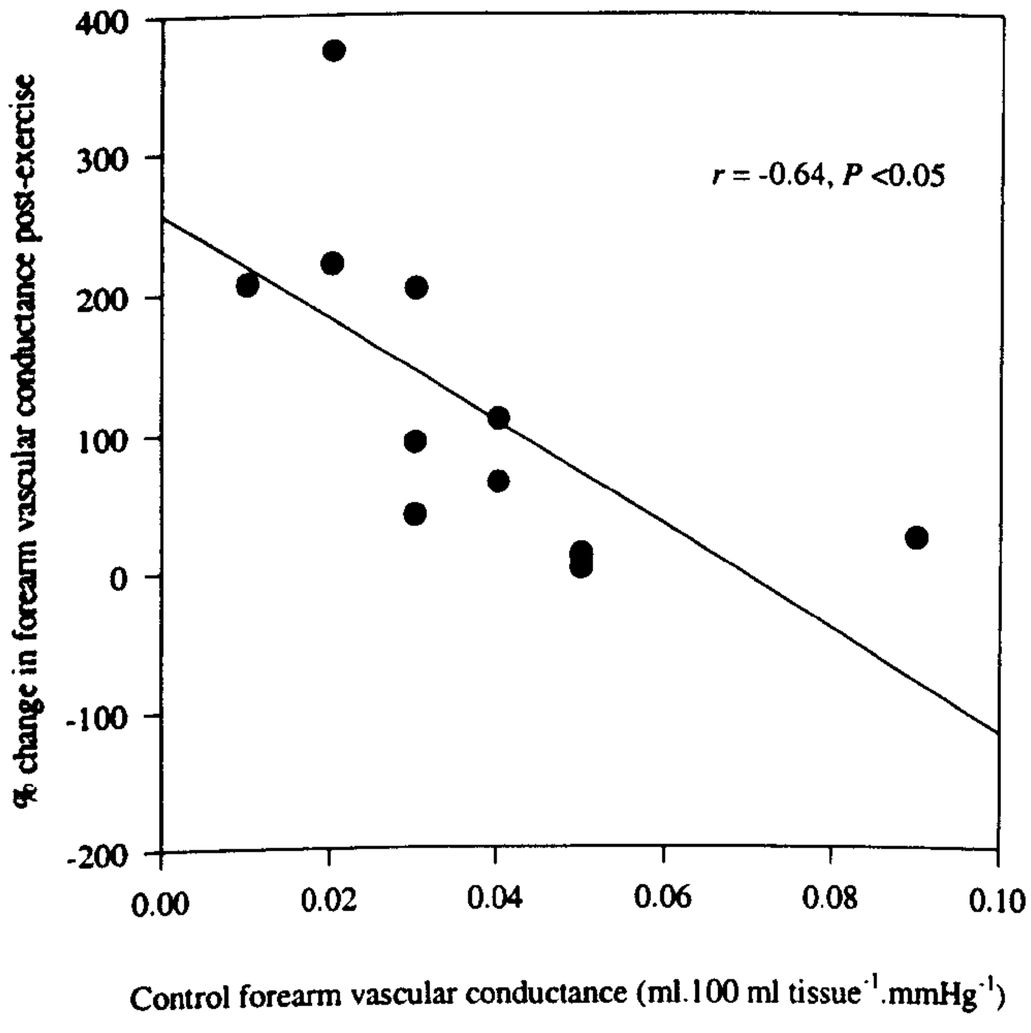


Figure 6.6b. Relationship between control forearm vascular conductance and percentage change in forearm vascular conductance post exercise.

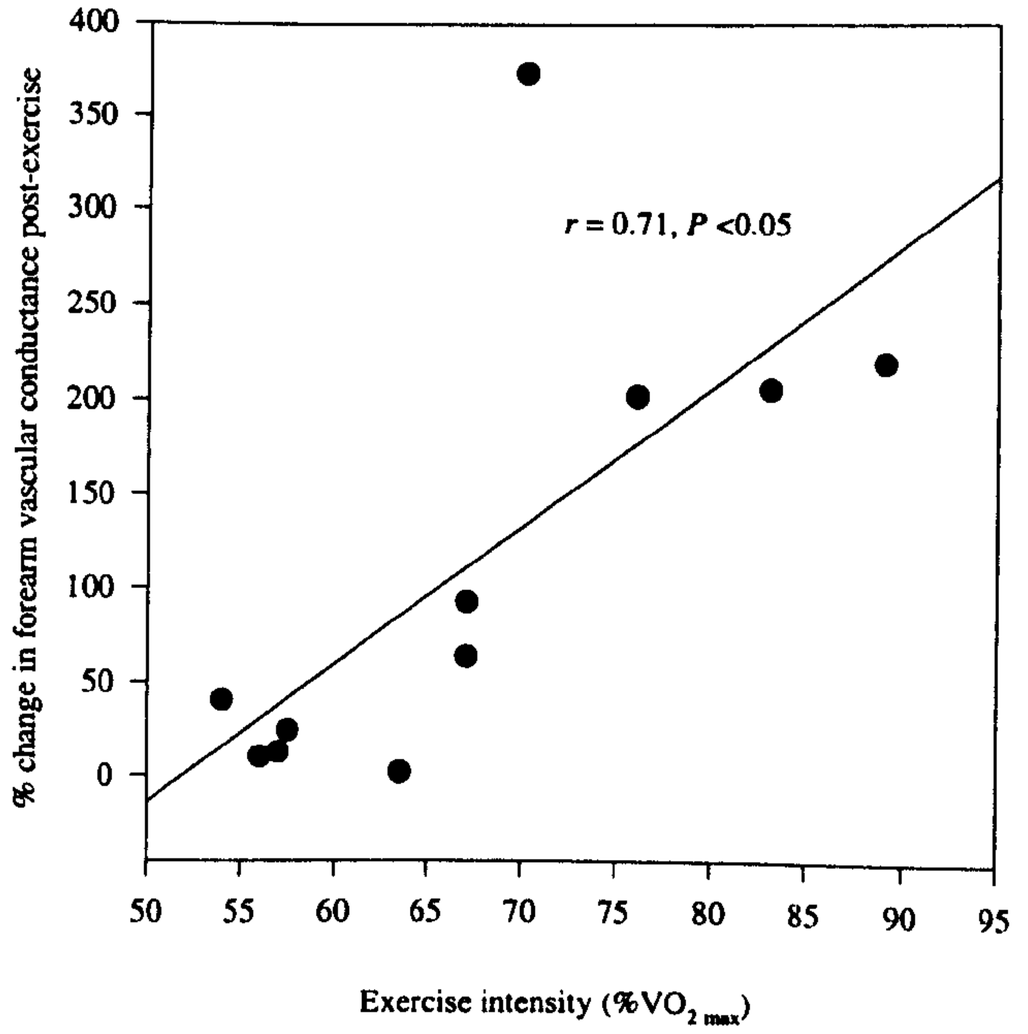


Figure 6.6d. Relationship between exercise intensity and percentage change in forearm vascular conductance post exercise.

Table 6.2. Cardiovascular responses at rest and during Stroop mental challenge after acute exercise (Post-ex) and control (Cntrl) conditions in males with a family history of hypertension (mean ± *SEM*).

Variable	Condition									
	Baseline		**Stroop** (0-2 min)		**Stroop** (5-6 min)		**Stroop** (9-10 min)		**Recovery**	
	Post-ex	Cntrl	Post-ex	Cntrl	Post-ex	Cntrl	Post-ex	Cntrl	Post-ex	Cntrl
HR ($b.min^{-1}$)	76.1±3	61.6±2#	89.1±3	74.0±2#	83.6±3	71.2±2#*	81.6±3	70.0±2#*	74.1±3	62.0±2#*
SV (ml)	80.4±4	92.5±5	67.1±4	78.3±4	73.4±5	83.7±5	75.7±5	85.6±5	82.0±4	93.8±4
CO ($l.min^{-1}$)	6.1±.3	5.6±.3	5.9±.3	5.8±.3	6.0±.3	5.9±.3	6.1±.3	5.9±.4	6.0±.3	5.8±.3
HPV_{ts} (.12-.4 Hz)	6.5±.4	8.2±.2#	4.6±.4	6.2±.3#	5.2±.4	6.6±.3#	5.3±.4	6.6±.3#	5.8±.3	7.2±.2#
HPV_{ts} (.07-.11 Hz)	2.5±.4	3.8±.2	1.8±.3	3.1±.2	2.2±.3	3.3±.2	2.3±.3	3.4±.2	2.7±.2	3.8±.2
PEP (ms)	80.5±3	77.4±3	77.4±4	73.9±3	76.9±3	74.0±3	75.8±3	75.1±4	76.9±3	76.2±4
LVET (ms)	291.3±6	311.3±5	274.2±6	295.5±4	282.5±8	300.9±5	285.0±7	301.7±5	295.5±6	312.2±5
PL ratio	0.3±.01	0.3±.01	0.3±.01	0.3±.01	0.3±.01	0.3±.01	0.3±.01	0.3±.01	0.3±.01	0.3±.01
HI ($ohm.s^{-2}$)	11.4±.8	12.7±.7	10.6±.8	11.7±.9	11.2±.8	12.3±.9	11.3±.8	12.2±.9	11.6±.8	12.5±.8
SBP (mmHg)	108.1±4	119.8±4#	126.7±4	133.7±4	126.5±4	137.8±5	124.3±3	136.4±5#	116.2±3	127.3±4#
DBP (mmHg)	58.1±3	64.5±3	71.7±3	75.3±2	71.5±2	77.8±3	70.8±2	76.0±3	65.2±2	70.2±3
MAP (mmHg)	74.4±3	82.6±3	89.7±3	94.5±3	89.5±3	97.4±4	88.4±2	95.9±3	81.9±2	88.9±3
RPP ($b.min^{-1}.mmHg$)	82.2±3	73.9±4	112.5±4	98.9±3	105.5±4	98.2±5	101.1±4	95.4±4	85.7±3	79.2±4
TPR ($dyne\text{-}s.cm^{-5}$)	1027.7±85	1236.8±92	1257.3±80	1354.8±82	1236.2±85	1374.8±98	1212.1±82	1351.9±98	1138.2±79	1283.7±88
FBF ($ml.100\ ml\ tissue^{-1}.min^{-1}$)	5.1±.5	3.1±.5	6.7±.6	5.6±.7*	-	-	6.8±.7	5.4±.8*	5.6±.5	3.9±.6
FVR ($mmHg.ml^{-1}.100\ ml\ tissue^{-1}$)	15.9±1	32.5±5#	14.6±1	19.8±2#*	-	-	14.3±1	22.7±3#*	16.4±2	28.5±4#
FVC ($ml.100\ ml\ tissue^{-1}.mmHg^{-1}$)	.070±.01	.039±.01#	.074±.01	.060±.01*	-	-	.078±.01	.059±.01*	.069±.01	.045±.01#

Significant difference in absolute values between conditions.
*Significant difference in change relative to baseline between conditions.

6.4 Discussion

The purpose of Study III was to investigate the effect of acute exercise on hemodynamic variables at rest and during mental stress in males with family history of hypertension. The major findings were a significant post-exercise hypotension response during recovery and a trend for lower BP during mental stress, which was characterised by a consistent reduction in FVR. Also, a post-exercise blunted vasodilatation reactivity response to stress was observed.

6.4.1 Effect of Acute Exercise on Resting Hemodynamics

Although post-exercise hypotension has been consistently demonstrated among hypertensive subjects (Bennett *et al.*, 1984; Cleroux *et al.*, 1992b; Floras *et al.*, 1989; Hagberg *et al.*, 1987; Quinn, 2000), a number of studies in normotensives have not displayed this response (Brownley *et al.*, 1995; Cleroux *et al.*, 1992b; Perronet *et al.*, 1989; Quinn, 2000; Rejeski *et al.*, 1992; Roy & Steptoe, 1991). For example, Cleroux *et al.* 1992b examined systemic hemodynamics for 3 hr after cycle ergometry exercise (30 min, 50% $\dot{V}O_{2max}$) in hypertensive and normotensive subjects. The hypertensive subjects demonstrated significant reductions in both SBP and DBP persisting for 3 hr post-exercise while the post-exercise BP of the normotensive subjects was unchanged. The major post-exercise hemodynamic differences between the groups was a lower TPR and FVR in the hypertensives, that was correlated with lower post-exercise plasma norepinephrine. That post-exercise hypotension, characterised by lower SBP, has been displayed in the present cohort of males with a family history of hypertension suggests that the response may only be apparent in individuals who are predisposed to certain patterns of cardiovascular functioning or have a specific response to exercise. For example, a number of studies have demonstrated that individuals with a family history of hypertension, compared to

those without, have a higher SBP response (Molineux & Steptoe, 1988; Nielson *et al.*, 1989; Saito *et al.*, 1989) and significantly higher venous norepinephrine levels (Wilson, Sung, Pincomb, & Lovallo, 1990) during submaximal exercise. The cardiovascular patterning responses closely related with hypertensives and offspring hypertensives is elevated levels of sympathetic nervous activity (SNA) that may explain why the mechanism most commonly associated with post-exercise hypotension is sympathoinhibition. Thus, it may only be in individuals with heightened sympathetic drive that a significant post-exercise hypotensive effect is observed.

6.4.1.1 Sympathoinhibition. Post-exercise sympathoinhibition is thought to involve both neural and local mechanisms. Although the present study did not employ any measures to directly assess sympathetic outflow to the vasculature, HPV_{ts} at medium frequencies was examined, which is thought to provide a measure of cardiac sympathetic activation. That HPV_{ts} at the medium frequencies was significantly blunted post-exercise suggests a cardiac sympathoinhibition response. Also, that HPV_{ts} at the high frequencies, thought to signify cardiac parasympathetic influence, was significantly blunted post-exercise suggests that elevated post-exercise HR was due to vagal withdrawal and not sympathetic activation. Floras *et al.* (1989) reported a decreased post-exercise SNA to the skeletal muscles of the leg measured with microneurography, in hypertensive subjects. A possible neural mechanism is an increased sympatho-inhibitory input from cardiopulmonary (C-P) baroreceptors post-exercise. Collins and DiCarlo (1993) showed that post-exercise hypotension was reversed in rats after blocking C-P afferents. Also, Bennett *et al.* (1984) examined FVR responses to LBNP before and after exercise. These authors reported greater increases in FVR during LBNP after exercise, suggesting that C-P baroreceptors exert

a greater inhibitory influence on the vasculature after exercise. Because dysfunction to the C-P baroreceptors has been reported in borderline hypertensives (Mark & Kerber, 1982) and offspring hypertensives (Ueda *et al.*, 1989) it is possible that exercise may have a greater effect on the baroreceptors in these groups.

The reduction in FVR observed post-exercise is similar to the findings of West *et al.* (1998) who observed consistent reductions in a vascular resistance index post-exercise that was greater in individuals with higher vascular resistance on the control day. That a post-exercise increase in baseline FBF was observed despite employing leg exercise is also in agreement with previous work (Cleroux *et al.*, 1992b). This suggests that local ischemic metabolites are not the only mechanism responsible for decreased vascular tone. In addition to reductions in neurally mediated sympathetic outflow, vascular responsiveness to α-adrenergic receptor stimulation is impaired after exercise (Halliwill, Taylor, & Eckberg, 1996). Local mechanisms that effect the transduction of sympathetic outflow at the level of arterial smooth muscle may include release of vasodilator substances, or by modulation of the α-adrenergic pathway (presynaptic or postsynaptic inhibiton), see Figure 6.7. Nitric oxide is a prime candidate as a local vasodilator because studies have shown it to be increased after acute exercise (Jungersten, Ambring, & Wennmalm, 1997) and it is also known to attenuate the vasoconstrictor response to α-adrenergic receptor stimulation (Patil, DiCarlo, & Collins 1993). Down-regulaton of α-adrenergic responsiveness may be important in hypertensives and offspring hypertensives because they have demonstrated exaggerated vascular or pressor responses, or lower threshold response to infused norepinephrine (Doyle & Fracerm, 1961; De Lima *et al.*, 1990).

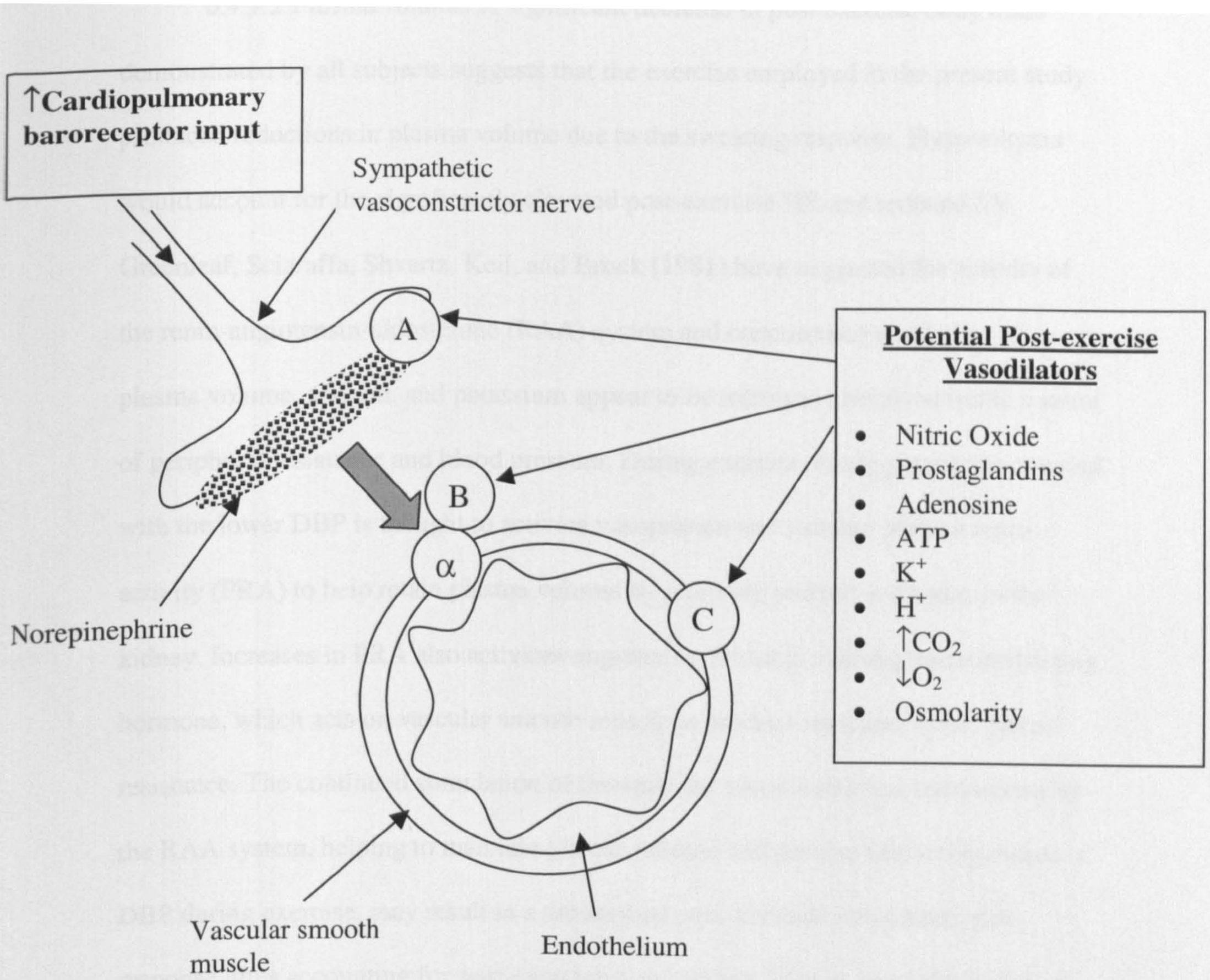


Figure 6.7. Neural and local control of vascular tone related to post-exercise hypotension. During post-exercise hypotension, diminished vasoconstrictor responses and vasodilatation may be produced by enhanced cardiopulmonary baroreceptor activity and vasodilator substances acting via presynaptic (A) or postsynaptic (B) modulation of the α-adrenergic pathway or by direct effects on smooth muscle relaxation (C). Adapted from Halliwill (2001).

6.4.1.2 Plasma volume. A significant decrease in post-exercise body mass demonstrated by all subjects suggests that the exercise employed in the present study produced reductions in plasma volume due to the sweating response. Hypovolemia would account for the significantly elevated post-exercise HR and reduced SV. Greenleaf, Sciaraffa, Shvartz, Keil, and Brock (1981) have suggested the activity of the renin-angiotensin-aldosterone (RAA) system and concomitant regulation of plasma volume, sodium, and potassium appear to be intimately involved in the control of peripheral resistance and blood pressure. During exercise, the hypovolemia coupled with the lower DBP is thought to activate vasopressin and increase plasma renin activity (PRA) to help retain plasma volume by retaining sodium and water in the kidney. Increases in PRA also activates angiotensin II that is a strong vasoconstricting hormone, which acts on vascular smooth muscle to produce increases in peripheral resistance. The continued stimulation of the vascular vasoconstrictive mechanism by the RAA system, helping to maintain plasma volume and prevent further decreases of DBP during exercise, may result in a diminished post-exercise vasoconstrictive response, thus accounting for post-exercise hypotension. That is, most physiological systems demonstrate a characteristic over compensation in order to restore homeostasis.

6.4.1.3 Thermoregulatory vasodilatation. Another possible mechanism involved in the post-exercise hypotensive response is thermoregulatory vasodilatation. An increased vasodilatation response in the skin could have contributed to a reduced post-exercise vascular resistance. The method employed in the present study specifically measured forearm muscle blood flow and it is therefore difficult to make inferences concerning forearm skin blood flow because the muscle and skin circulation are thought to be under different regulatory control. However, Cleroux *et*

al. (1992b) evaluated post-exercise forearm skin blood flow in hypertensive and normotensive subjects by measuring blood flow to the hand, as most of the blood flow to the hand is distributed to the skin. That only the hypertensive group demonstrated post-exercise hypotension, yet both groups demonstrated similar post-exercise reductions in hand vascular resistance, suggests that the skin vasodilatation response does not play a major role in post-exercise hypotension. In contrast, Franklin, Green, and Cable (1993) demonstrated that the magnitude of post-exercise hypotension was dependent on the environmental conditions during recovery from exercise. Post-exercise hypotension was greater when subjects recovered in warm conditions compared with neutral and cool climates suggesting that part of the hypotensive effect may be dependent upon thermoregulatory-induced changes in skin blood flow. That subjects in the present study recovered from exercise in a warm climate (24°C) suggests that thermoregulatory vasodilatation may have played some part in the post-exercise hypotension response.

6.4.2 Hypotensive Effects and Exercise Intensity

The present findings suggest that there is a strong relationship between post-exercise reduction in FVR and exercise intensity. Previous work by Steptoe *et al.* (1993) examined the effect of high (70% $\dot{V}O_{2max}$) and moderate intensity (50% $\dot{V}O_{2max}$) exercise on cardiovascular responses following exercise. The authors demonstrated that both exercise intensities significantly reduced SBP in comparison with baseline by similar levels (10.2 versus 6.9 mmHg reductions in SBP for 70 and 50% exercise intensities respectively). However, baroreflex sensitivity, assessed from the naturally occurring covariations of SBP and pulse interval, was significantly lower following exercise in the 70% condition compared with both 50% and control conditions. Cleroux *et al.* (1992a) speculated that post-exercise facilitation of an

inhibitory C-P reflex effect might be responsible for resetting the arterial baroreflex. That is, enhanced neural activity from C-P baroreceptors entering the central nervous system may alter the operating point of the arterial baroreflex. Thus, this supports the notion that at higher exercise intensities arterial baroreflex sensitivity may be depressed post-exercise due to increased C-P baroreceptor input, causing enhanced reductions in FVR. Factors contributing to the facilitation of inhibitory C-P reflexes following exercise are thought to be largely through changes in contractility mediated through changes in circulating catecholamine concentration and the SNS (DiCarlo *et al.*, 1994). Thus, an enhanced level of C-P input post-exercise, as a result of higher exercise intensities may be due to an increase in cardiac contractility induced by increases in circulating catecholamines.

Hard exercise is also associated with a greater depletion of plasma volume and that the catecholamines are also known to stimulate PRA suggests that at higher exercise intensities the RAA system response might be exaggerated. Thus, greater vasconstrictive effects might be produced during exercise promoting larger decreases in FVR post-exercise.

6.4.3 Effect of Acute Exercise on Stress Reactivity

The present findings of a blunted BP response to the mental stress, post-exercise are consistent with previous research (Probst *et al.*, 1997; Rejeski *et al.*, 1991; Roy & Steptoe, 1991; Steptoe *et al.*, 1993; West *et al.*, 1998). The cardiovascular patterning suggests that the blunted BP response was not due to a central mechanism, as the post-exercise absolute HR levels were significantly elevated throughout the Stroop. Although data from the present study demonstrates a significantly lower HR reactivity to the second part of Stroop post-exercise, compared with control, this may have been confounded by an already elevated post-exercise

HR. This data is similar to that of Probst *et al.* (1997) who also observed a blunted HR response to the Stroop post-exercise, but also had elevated post-exercise HR. Although the present findings and those of Probst *et al.* (1997) may have been confounded by elevated baseline post-exercise HR, there is evidence to suggest HR responsiveness is reduced after acute exercise in dogs (Friedman, Ordway, & Williams, 1987). Friedman *et al.* (1987) showed that after 60 min of treadmill running at 60-80% maximum HR, dogs exhibited functional desensitisation of β-1 adrenergic receptors evidenced by a three-fold increase in the dose of isoproterenol required to produce a 25 $b.min^{-1}$ increase in HR. However, data from the present study is more supportive of a peripheral mechanism to explain the blunted BP response. This was demonstrated by a significantly reduced FVR throughout Stroop, post-exercise. That the percentage change in FBF during Stroop was significantly lower post-exercise in comparison with control suggests an exercise-induced reduction in vascular reactivity.

The skeletal muscle vasodilatation response to mental stress is thought to involve both sympathetic withdrawal and β-2 adrenergically mediated vasodilatation (Halliwill *et al.*, 1997). That a post-exercise vasodilatation response was already apparent before the start of the stress task, which was probably due to reductions in α-adrenergic tone (sympathetic withdrawal), suggest that the post-exercise vasodilatation response to stress was possibly completely mediated by β-2 adrenergic pathways. Therefore, a blunted vasodilatation stress response post-exercise was possibly due to a combination of reduced sympathetic withdrawal and down regulation of β-2 adrenergic receptors. The data from Study I supports a role for the C-P baroreptors in the vasodilatation stress response because when LBNP was used to unload these receptors the vasodilatation stress response was attenuated. In the present study, as previously discussed, C-P baroreceptor input was probably already increased

as a result of acute exercise and therefore this may have negated any further increases in baroreceptor activity during stress. There is also strong evidence for down regulation of the β-2 adrenergic receptors. Butler, Kelly, O'Mally, and Pidgeon (1983) showed that an acute bout of exercise in man resulted in an immediate increase in β-2 adrenoceptor responsiveness that was rapidly followed by a desensitisation 25 min post-exercise. Howard and DiCarlo (1992) also demonstrated an attenuated response of the vasculature to β-2 adrenergic receptor mediated vasodilatation after acute exercise in rabbits. Howard and DiCarlo (1992) suggested the mechanism may be related to high levels of active hormones, increased body temperature, local acidosis, and increasing levels of PCO_2 as these factors are known to occur as a result of acute exercise. For example, exposure of target cells to high concentrations of a hormone results in subsequent decreases in sensitivity (Lefkowitz, Caron, & Stiles, 1984). Thus, during exercise when epinephrine is significantly increased, this may result in a functional downregulation of the β-2 adrenergic receptor post-exercise. Also, researchers have reported attenuated adrenergic receptor sensitivity at temperatures above 23°C (Roberts, Chilgren, & Zygmunt, 1989) and under conditions of acidosis (Stokke *et al.*, 1984). A reduction in epinephrine discharge from the adrenal medulla, post-exercise, may further reduce the β-adrenergically mediated vasodilatation stress response. Peronnet *et al.* (1989) demonstrated a 50% reduction in plasma epinephrine post-exercise during the Stroop mental challenge. See Figure 6.8.

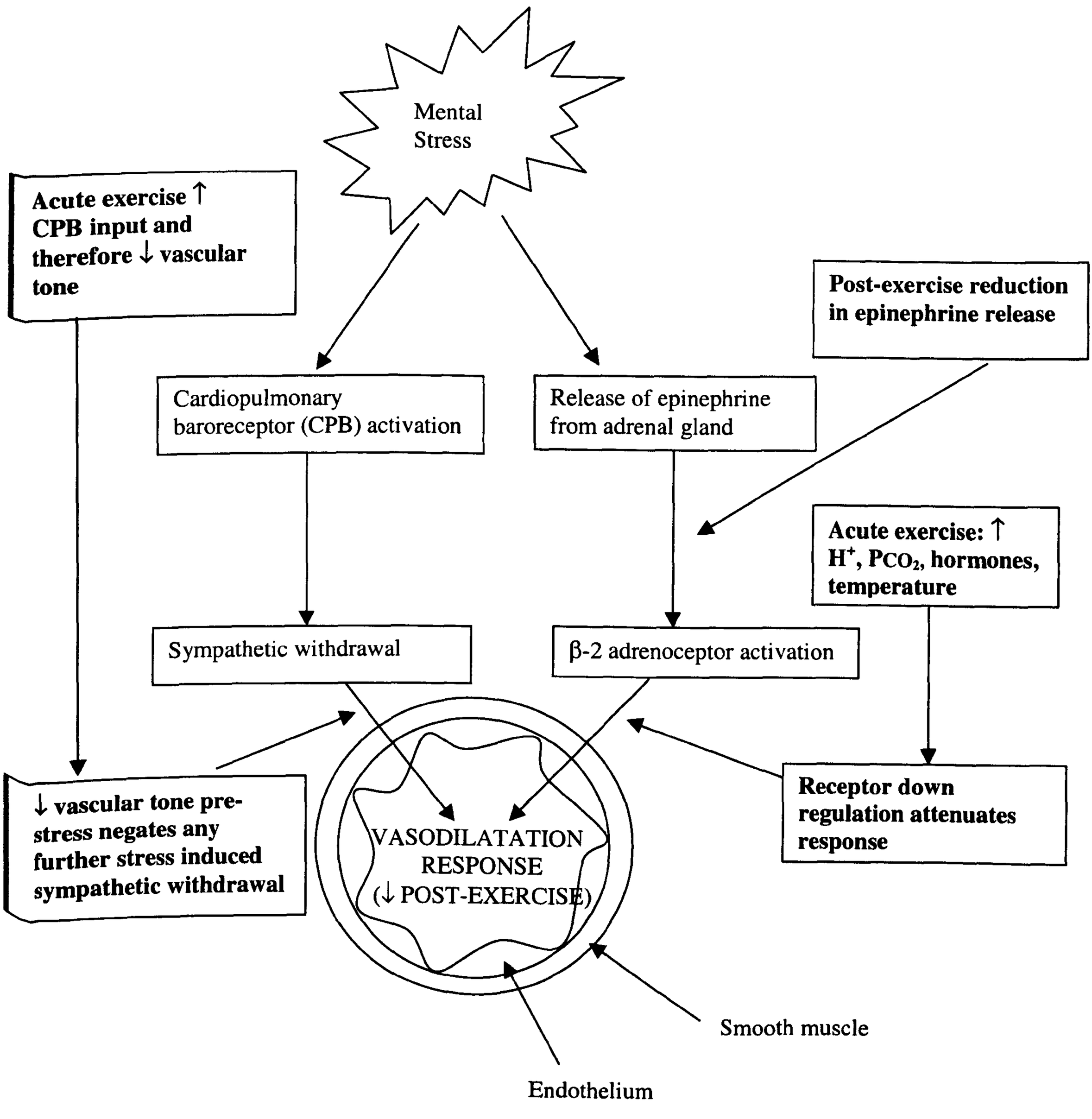


Figure 6.8. Model for the effect of acute exercise on forearm vasodilatation response to stress.

6.4.4 Interaction of the Opioid Pathways

Another possible mechanism that has been linked to post-exercise sympathoinhibition and reduced stress reactivity is the opioid receptor pathways in the central nervous system (Thoren, 1990). Morris *et al.* (1990) showed that an opiate antagonist enhanced HR reactivity to a mental stress task, although it had no effect on blood pressure response or plasma catecholamine levels. Schobel, Oren, Mark, and Ferguson (1992) showed that the opioid antagonist, naloxone, selectively potentiates C-P baroreflex regulation of sympathetic neural activity during lower body negative pressure from 0 to -15 mmHg in humans. Weinstock and Weksler-Zangen (1989) have also shown that low baroreflex sensitivity was due to deficient opioid inhibition of sympathetic outflow in rabbits. However, further studies have indicated that post-exercise SNA is not altered using an opiate antagonist (Hara & Floras, 1992) which casts doubts on the mechanism.

6.4.5 Implications

Reducing vascular reactivity in individuals at risk from hypertension may be particularly important because numerous daily episodes of excessive regional blood flow may be responsible for a vascular re-modelling process that has been linked to the development of hypertension. That the catecholamines are thought to possess trophic properties, which may enhance the growth of vascular smooth muscle (Blaes & Boissel, 1983) suggests that hyper-reactivity of the SNS may play a significant role in the vascular remodelling process. The administration of β-blockers in man and animals is associated with regression of vascular hypertrophy (Franklin, Morris, & Loveday, 1982; Hansson & Sivertsson, 1984). This suggests β-blockers may interrupt the adrenergic mechanism causing hypertrophy. This is supported by findings that show β-blockers prevent growth of smooth muscle cells in culture (Yamori *et al.*,

1984) and that denervation reduces the extent of vascular hypertrophy in hypertension by a mechanism independent of pressure (Hart, Heistad, & Brody, 1980). Thus, an exercise-induced sympathoinhibition and down regulation of β-adrenergic receptors may play an important role in preventing changes to cardiovascular functioning associated with early stages in the developmental process of hypertension.

6.4.6 Summary

A bout of strenuous acute exercise has produced a hypotensive BP response during recovery and a trend for lower BP during mental stress, which was characterised by a consistent reduction in FVR. Also, a blunted FBF reactivity response to stress, post-exercise, has been demonstrated.

CHAPTER 7

GENERAL DISCUSSION AND FURTHER RESEARCH

Three studies have been completed that have investigated the effects of physical activity and acute exercise on risk markers of hypertension in male offspring hypertensives. This general discussion will firstly summarise the major findings by reviewing the hypotheses, then outline the implications and importance of the results, and finally make overall conclusions and suggestions for further work.

7.1 Review of Hypotheses

7.1.1 Study I

The hypothesis stating that moderately active offspring hypertensives would display augmented cardiopulmonary baroreceptor function compared with highly active offspring hypertensives was partially accepted because although augmented function was not observed at rest, it was observed during mental stress. The second hypothesis that stated moderately active offspring hypertensives would display a higher level of cardiovascular reactivity in comparison with the highly active offspring hypertensives was accepted. Specifically, the moderately active group displayed greater levels of cardiac and forearm blood flow (FBF) reactivity to mental challenge. These findings were related to hyper-reactivity of the sympathetic nervous system.

7.1.2 Study II

The hypothesis stating moderately active offspring hypertensives would display urinary sodium retention during mental challenge in comparison with the highly active offspring hypertensives was not accepted. However, the second hypothesis stating that moderately active offspring hypertensives would display a higher level of cardiovascular reactivity to an extended mental challenge in

comparison with the highly active offspring hypertensives was accepted. Specifically, FBF reactivity was greater in the moderately active during the initial stages of the stress, although both groups displayed enhanced FBF for the whole stress period. Differences in sympatho-adrenal responses and/or β-2 adrenergic receptor sensitivity between the moderately and highly active groups were implicated in these findings.

7.1.3 Study III

The hypothesis stating that acute exercise would lower cardiovascular reactivity to mental challenge in offspring hypertensives was accepted. Specifically, there was a trend for lower blood pressure (BP) during stress post-exercise and FBF reactivity was diminished following acute exercise in comparison with control conditions. Post-exercise sympathoinhibition and a possible down regulation of β-2 adrenoceptors were implicated in these findings.

7.2 Implications and Importance of Findings

The β-2 adrenoceptors have been identified in the present research as playing a key role in the hyper-reactive response to stress and have been strongly implicated in a pathological vascular re-modelling process. Recent work has tested the hypothesis that genetic variation in the β-2 adrenoceptor gene is associated with a genetic predisposition to hypertension. Timmermann *et al.* (1998) demonstrated that the Arg16 variant of the β-2 adrenoceptor was associated with parental hypertension and higher BP in a sample of 23 hypertensive and 22 normotensive northern European families. Bengtsson *et al.* (2001) also showed that individuals with type II diabetes who possessed the Arg16 variant of the β-2 adrenoceptor appeared to be at increased risk of hypertension in a sample of hypertensive patients with and without type II diabetes, and healthy control subjects. The functional importance of the Arg16 variant has been demonstrated in two contrasting studies. Firstly, Hoit, Suresh, Craft, Walsh,

and Liggett (2000) studied the vasodilatation response to the β-2 agonist terbutaline in individuals who possessed the Arg16 variant or the Gly16 variant of the β-2 adrenoceptor gene. They concluded that in individuals possessing the Gly16 variant the vasodilatation response to catecholamines was attenuated in comparison with the Arg16 variant. However, in contrast Cockcroft *et al.* (2000) demonstrated that individuals with Arg16 variant of the β-2 adrenoceptor gene had attenuated vasodilatation responses to β-2 agonists in comparison with individuals possessing the Gly16 variant. Although this is a developing area of research that clearly needs further work, these studies confirm that there may be an important link between adrenoceptor polymorphisms and hypertension development. Specifically, there is evidence to suggest the Arg16 variant of the β-2 adrenoceptor gene is related to hypertension development and this variant may also be involved with exaggerated vasodilatation responses.

The possible interaction of exercise with the β-adrenoceptor at a molecular level was highlighted by Fujii *et al.* (1997) who examined the effect of acute exercise on β-adrenoceptor gene expression. The authors found that immediately after an incremental exercise test to exhaustion there was a significant increase in β-adrenoceptor number that was correlated to β-adrenoceptor mRNA level. Thus with future technological advancements in this area, research may identify specific effects of exercise on adrenoceptor polymorphisms.

7.3 Conclusions

Previous research has demonstrated that only 30-40% of offspring hypertensives actually develop hypertension (Watt, Foy, Holton, & Edwards, 1991). Although this figure increases with a bi-parental history of hypertension this suggests that despite the existence of certain risk markers, there are possibly a cluster of factors

that trigger the initial onset of hypertension development. For example, Dluhy, Hopkins, Hollenburg, Williams, and Williams (1988) have referred to "non-modulators" who are individuals that fail to modulate their renal blood flow and aldosterone responsiveness when dietary sodium is changed. Furthermore, non-modulation was also found to significantly aggregate in families with a history of hypertension. Other researchers (Miller *et al.*, 1995) have also shown an elevated total peripheral resistance and norepinephrine response to stress during sodium loading relative to placebo, in offspring hypertensives relative to controls. Therefore, it may be the combination of a number of lifestyle factors, such as a high sodium diet, lack of physical activity, and stress that provide the trigger for the development of hypertension in genetically predisposed individuals.

The present series of studies have clearly shown a strong association between aerobic exercise and cardiovascular reactivity to mental challenge in offspring hypertensives. The results suggest that exercise may be a suitable non-pharmacological intervention to reduce cardiovascular reactivity to stress, which has been linked to the development of hypertension. The present findings are supportive of a mechanism that is related to an acute as opposed to a chronic exercise stimulus, which may have important implications for future research.

7.4 Suggestions for Further Research

7.4.1 Acute Exercise Dose-response and Modality

The majority of research to date that has examined the anti-hypertensive and stress reactivity reducing effects of exercise has focused on chronic exercise training. Thus, although the optimal dose-response relationship between exercise and BP reduction is seemingly established for chronic exercise training, this is not the case for acute exercise. Two studies that have addressed the issue of dose-response

relationship and acute exercise in normal subjects (Rejeski *et al.*, 1991; Steptoe *et al.*, 1993) have suggested that rigorous exercise (70-80% $\dot{V}O_{2max}$) is more effective in attenuating psychophysiological reactivity during stress in comparison with moderate exercise (50% $\dot{V}O_{2max}$). However, both exercise intensities seemed to produce similar post-exercise hypotensive effects. Similarly, Quinn (2000) demonstrated that bouts of exercise at 50 and 75% $\dot{V}O_{2max}$ produced the same degree of post-exercise hypotension in hypertensive subjects. However, 24 hr ambulatory BP monitoring after the exercise bout demonstrated that both systolic and diastolic BP were reduced for a significantly longer period of time after the higher intensity exercise. This seems to be in contrast to the chronic training literature where a recent meta-analysis by Hagberg and Brown (1995) suggested that mild-moderate exercise is more effective for reducing high blood pressure. Thus, more research that addresses the dose-response relationship between acute exercise and attenuation of BP in hypertensive patients should be performed to identify potential mechanisms. Also, there is presently no other research in the literature, to the knowledge of the present author, which has examined the effects of acute exercise on FBF reactivity to stress. Thus, the current findings on the effects of acute exercise on FBF stress reactivity should be expanded. For example, the dose response relationship between acute exercise and FBF stress reactivity should be examined.

There is also little research that has examined the effect of exercise modality on the BP and stress reactivity lowering mechanisms of acute exercise. For example, the majority of exercise programmes currently prescribed in the health and fitness setting involve a combination of aerobic dynamic exercise and resistance exercises. However, there are few studies that have compared the acute effects of resistance training and aerobic exercise on post-exercise BP responses. MacDonald *et al* (1999)

showed that the post-exercise hypotension response was independent of exercise modality when comparing cycle ergometry exercise (15 min, 65% $\dot{V}O_{2max}$) with unilateral leg press resistance exercise (15 min, 65% of 1 repetition maximum), although employing a weak experimental design. MacDonald, MacDougall, and Hogben (2000) also demonstrated similar findings when comparing arm versus leg ergometry exercise (30 min, 65% VO_{2max}). However, there is no research that has examined the acute effect of exercise modality on stress reactivity. Therefore, further research is clearly needed in this area firstly to confirm the findings of MacDonald *et al* (1999) that resistance exercise contributes to an antihypertensive effect. Secondly, further research is needed to examine the antihypertensive mechanisms for different types of exercise that will contribute to the overall understanding of the effects of acute exercise on the cardiovascular responses.

7.4.2 Population Specific Research

Previous research has suggested that hypertensive subjects demonstrate significantly greater post-exercise reductions in BP compared with normotensive subjects, who sometimes do not demonstrate any significant reduction at all (Cleroux *et al.*, 1992b; Quinn, 2000). However, although the present research is the first to examine the post-exercise BP response in individuals with a family history of hypertension, further research should compare the response in both offspring hypertensives and offspring normotensives. This would provide further insight into individual variations in post-exercise cardiovascular responses.

7.4.3 Longitudinal Research and Risk Markers

Longitudinal research that follows families with a history of hypertension is of prime importance in order to elucidate the cluster of risk markers that are responsible for the early development of hypertension.

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APPENDICES

Appendix IA Informed Consent

SUBJECT INFORMED CONSENT

The researchers conducting this project support the principles governing both the ethical conduct of research, and the protection at all times of the interests, comfort, and safety of subjects.

This form and the accompanying "Information for Subjects" leaflet are given to you so that you may be fully informed of the experimental procedures and possible risks that accompany participation in this study.

Your signature below indicates six things:

(1) you have received the "Information for Subjects" leaflet;
(2) you have read its contents;
(3) you have been given the opportunity to discuss the contents with one of the researchers prior to commencing the experiment;
(4) you clearly understand the procedures and possible risks of participation in the study;
(5) you voluntarily agree to participate in the project; and
(6) your participation may be terminated at any point in time without jeopardising in any way your involvement with De Montfort University, or your assessment for any course undertaken through this university.

Any concerns, complaints, or further questions may be directed to Mark Hamer (The Physical Activity & Health Research Unit: phone 01234 793465), or Dr. Steve Boutcher (research supervisor: phone 01234 793353). Subsequent inquiries may be directed to Simon Eassom (Director of the Human Ethics Committee: phone 01234 793373).

Signed:_____ Date:_____

Appendix IB Study I Information Sheet

THE PHYSICAL ACTIVITY AND HEALTH RESEARCH UNIT
DE MONTFORT UNIVERSITY, BEDFORD

INFORMATION FOR SUBJECTS

1. *Project Objectives.* To identify risk markers of hypertension in high risk individuals.

2. *Rationale.* Hypertension presents a serious health concern to the worldwide population. The identification of early risk markers to predict the future development of hypertension is therefore an important and ongoing area of research.

3. *Test Procedures.* Testing will involve the application of surface electrodes and electrode band tape to the upper body, a blood pressure cuff on the left arm, wrist, arm cuffs and a mercury strain gauge on the right arm. The collection of data will involve lying down in a supine position, with the lower body sealed in a lower body negative pressure chamber. Measurements of heart rate, cardiac output, stroke volume, blood pressure and forearm blood flow will be taken. The experimental procedure will involve the application of mild levels of lower body negative pressure (stimulates standing up from sitting), a word colour identification test, and a cold pressor test involving application of ice to the forehead for 1-min. Subjects will be required to undergo a maximal oxygen uptake test on a bicycle ergometer, lasting approximately 10-min.

4. *Risks and Discomforts.* During the experimental session it is anticipated that your heart rate and blood pressure will rise, although not to levels higher than you would commonly experience. Application of lower body negative pressure will produce sensations similar to standing up from a supine position. The word-colour identification task may induce mild psychological stress, and the cold pressor test may cause a certain degree of discomfort. During the maximal exercise test you may feel a certain amount of discomfort in the legs and chest, but this is quite normal.

5. *Inquires.* Questions concerning the procedures and/or rationale used in this study are welcome at any time. All initial inquiries should be directed to the investigator conducting this project (Mark Hamer, The Physical Activity & Health Research Unit: phone 01234 793465), or Dr. Steve Boutcher (research supervisor: phone 01234 793353).

6. *Freedom of Consent.* Participation in this project is entirely voluntary. You are free to deny consent before or during the experiment. In the latter case such withdrawal of consent should be made at the time you specify, and not at the end of a particular trial. Your participation and/or withdrawal of consent will not influence your present and/or future involvement with De Montfort University. In the case of student involvement it will not influence grades awarded by the University.

7. *Confidentiality.* All questions, answers, and results of this study will be treated with absolute confidentiality. Subjects will be identified in the resultant manuscripts, reports or publications by the use of subject codes only.

Appendix IC Medical History Questionnaire

Physiology of Exercise Laboratories
Alexander Sports Hall
Sidney Road
BEDFORD MK40 2BQ

DE MONTFORT
UNIVERSITY
BEDFORD

PRE-TEST MEDICAL QUESTIONNAIRE

Name: .....

Date of Birth ..... Age: ..... Sex: .....

Please answer the following questions by putting a circle round the appropriate response or filling in the blank.

I. How would you describe your present level of activity?
Sedentary / Moderately active / Active / Highly active

2. How would you describe your present level of fitness?
Unfit / Moderately fit / Trained / Highly trained

3. How would you consider your present body weight?
Underweight / Ideal / Slightly over / Very overweight

4. Smoking Habits:

Are you currently a non-smoker?	Yes/No
Are you a previous smoker?	Yes/No
How long is it since you stopped?	... years
Were you an occasional smoker?	Yes / No
	... per day
Were you a regular smoker?	Yes/ No
	... per day

5. Do you drink alcohol? Yes / No
If you answered Yes, do you have:
An occasional drink / a drink every day / more than one drink a day?

6. Have you had to consult your doctor within the last six months? Yes / No
If you answered Yes, please give details to the tester.

7. Are you presently taking any form of medication? Yes / No
If you answered Yes, please give details to the tester.

8. As far as you are aware, do you suffer or have you ever suffered from:

a. Diabetes? Yes /No b. Asthma? Yes /No

c. Epilepsy? Yes /No d. Bronchitis? Yes /No

e. Any form of heart complaint? Yes /No f. Serious back or neck injury? Yes/No

g. High blood pressure Yes /No h. Aneurysm or embolism? Yes/No

9. Is there a history of heart disease in your family?

10. Do you currently have any form of muscle or joint injury? Yes / No

11. Have you had to suspend your normal training in the last two weeks? Yes / No

12. As far as you are aware, is there anything that might prevent you from successfully completing the tests that have been outlined to you? Yes / No

13. As far as you are aware:

a. Are you suffering from any known active, serious infection?

b. Have you had jaundice within the previous year?

c. Have you ever had any form of hepatitis?

d. Are you HIV antibody positive?

e. Have you ever been involved in intravenous drug use?

f. Are you a man who has had any sexual contact with another man?

g. Have you had unprotected sexual intercourse with any person from an HIV high risk population e.g. Africa, Thailand, Miami since 1977?

h. Are you a haemophiliac?

i. Have you ever been a prostitute? (male or female)

j. Have you had sexual partners of categories d – i above?

If you can answer yes to any of questions a - i, please sign here:

.....

If you have answered no to all of questions a - i, please sign here:

.....

If there is any change in circumstances outlined above, it is your responsibility to the person administering the test immediately.

Appendix ID Physical Activity Readiness Questionnaire

PHYSICAL ACTIVITY READINESS QUESTIONNAIRE (PAR-Q)
A Self-administered Questionnaire for Adults

PARTICIPANT IDENTIFICATION

PAR-Q & YOU

PAR-Q is designed to help you help yourself. Many health benefits are associated with regular exercise, and the completion of PAR-Q is a sensible first step to take if you are planning to increase the amount of physical activity in your life.

For most people physical activity should not pose any problem or hazard. PAR-Q has been designed to identify the small number of adults for whom physical activity might be inappropriate or those who should have medical advice concerning the type of activity most suitable for them.

Common sense is your best guide in answering these few questions. Please read them carefully and check the ❑ YES or NO opposite the question if it applies to you.

YES	NO		
❑	❑	1	Has your doctor ever said you have heart trouble?
❑	❑	2	Do you frequently have pains in your heart and chest?
❑	❑	3	Do you often feel faint or have spells of severe dizziness?
❑	❑	4	Has a doctor ever said your blood pressure was too high?
❑	❑	5.	Has your doctor ever told you that you have a bone or joint problem such as arthritis that has been aggravated by exercise, or might be made worse with exercise?
❑	❑	6.	Is there a good physical reason not mentioned here why you should not follow an activity program even if you wanted to?
❑	❑	7.	Are you over age 65 and not accustomed to vigorous exercise?

IF YOU ANSWERED

YES to one or more questions

If you have not recently done so, consult with your personal physician by telephone or in person BEFORE increasing your physical activity and/or taking a fitness test. Tell him what questions you answered YES on PAR-Q, or show him your copy.

programs

After medical evaluation, seek advice from your physician as to your suitability for:

- unrestricted physical activity, probably on a gradually increasing basis.
- restricted or supervised activity to meet your specific needs, at least on an initial basis. Check in your community for special programs or services.

NO to all questions

If you answered PAR-Q accurately, you have reasonable assurance of your present suitability for:

- A GRADUATED EXERCISE PROGRAM. A gradual increase in proper exercise promotes good fitness development while minimizing or eliminating discomfort.
- AN EXERCISE "FITNESS" TEST. Simple tests of fitness (such as the Canadian Home Fitness Test) or more complex types may be undertaken if you so desire.

postpone

If you have a temporary minor illness, such as a common cold.

Figure 3.1 The Physical Activity Readiness Questionnaire (PAR-Q) is useful in health fair or mass testing situations for screening out individuals at risk for cardiovascular or metabolic disease.[1]

Appendix IE　State-Trait Anxiety Inventory Form X-1

SELF-EVALUATION QUESTIONNAIRE

Developed by C. D. Spielberger, R. L. Gorsuch and R. Lushene

STAI FORM *X-1*

NAME_____

CODE:_____ DATE:_____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel right now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	①	②	③	④
2. I feel secure.	①	②	③	④
3. I am tense	①	②	③	④
4. I am regretful	①	②	③	④
5. I feel at ease...	①	②	③	④
6. I feel upset..	①	②	③	④
7. I am presently worrying over possible misfortunes.	①	②	③	④
8. I feel rested...	①	②	③	④
9. I feel anxious.	①	②	③	④
10. I feel comfortable.	①	②	③	④
11. I feel self-confident.....	①	②	③	④
12. I feel nervous.	①	②	③	④
13. I am jittery.	①	②	③	④
14. I feel "high strung"	①	②	③	④
15. I am relaxed.....	①	②	③	④
16. I feel content.	①	②	③	④
17. I am worried..	①	②	③	④
18. I feel over-excited and "rattled"...	①	②	③	④
19. I feel joyful.....	①	②	③	④
20. I feel pleasant.	①	②	③	④

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Appendix IF 7-day Physical Activity Recall Questionnaire

The Seven-Day Recall

7 Participant_____

is_____ Today's Date_____

0. No (Skip to Q#4) 1. Yes

____ days

____ hours last week

WORKSHEET

		DAYS						
	SLEEP	1 __	2 __	3 __	4 __	5 __	6 __	7 __
MORNING	Moderate							
	Hard							
	Very Hard							
AFTERNOON	Moderate							
	Hard							
	Very Hard							
EVENING	Moderate							
	Hard							
	Very Hard							
Total Min Per Day	Strength:							
	Flexibility:	____	____	____	____	____	____	____

4a. Compared to your physical activity over the past three months, was last week's physical activity more, less or about the same?

1. More
2. Less
3. About the same

Worksheet Key:

An asterisk (*) denotes a work-related activity.
A squiggly line through a column (day) denotes a weekend day.

Rounding: 10-22 min.=.25 1:08-1:22 hr/min.=1.25
23-37 min.=.50
38-52 min.=.75
53-1:07 hr/min. =1.0

Notes

Example calculation

Sleep: 60.0 hr × 1 MET = 60 kcal.kg^{-1}

Light: 99.5 hr × 1.5 MET = 149 kcal.kg^{-1}

Moderate: 3.5 hr × 4 MET = 14 kcal.kg^{-1}

Hard: 2.5 hr × 6 MET = 15 kcal.kg^{-1}

Very hard: 2.5 hr × 10 MET = 25 kcal.kg^{-1}

Total weekly energy expenditure = 263 kcal.kg^{-1}.wk^{-1}

Total daily energy expenditure = 37.8 kcal.kg^{-1}.d^{-1}

Activity Intensity Classification

Sleep: defined as the time you get into bed to the time you get out of bed.

Moderate: similar to how you would feel when walking at a normal pace.

Hard: harder than walking but not as strenuous as running.

Very hard: similar to how you would feel when running.

Light: the remainder of time spent when not physically active or sleeping.

Appendix IG Study I Protocol

STUDY I: EXPERIMENTAL PROTOCOL

Activity	Time
Warm–up/check & calibrate equipment (COP, AMLAB, Impedance, Plethysmograph, Mass Spectrometer, LBNP chamber)	**1hr pre-test**
Subject physical screening	**(20 min)**
Informed consent, PAR-Q, medical questionnaire, STAI, 7-d. PAR	
Outline procedures of experiment and familiarise with Stroop	
Measurement of height, weight, body fat	
Subject preparation	**(20 min)**
Standing: fit impedance tape, ECG electrodes	
Supine: seal subject in LBNP chamber, measure BP (manually)	
attach ECG and impedance leads,	
attach Finapress and start (left hand)	
attach forearm strain gauge and occlusion cuffs (right arm positioned at 20°)	
Supine rest (10 min)	
Baseline measurements (supine)	**00-06 min**
Start Collection of HR, BP, CO	00:00
Normal breathing	00:00-03:00
Paced breathing	03:00-06:00
LBNP protocol	**06-15 min**
Inflate wrist cuff to 180 mmHg	06:00
Start arm occlusion	06:50
Collection of first 5 s FBF data	07:00
(collected for 5 s, every 10 s thereafter)	
Baseline	07:00-08:00
LBNP @ -5 mm Hg	08:00-09:30
LBNP @ -10 mm Hg	09:30-11:00
LBNP @ -15 mm Hg	11:00-12:30
LBNP @ -20 mm Hg	12:30-14:00
Release cuff pressure and stop collection of FBF data	14:00
Graded ↓ LBNP back to baseline (-1mmHg / 2 s)	14:00-15:00
Recovery	**15-20 min**
Stress protocol	**20-27 min**
Inflate wrist cuff to 180 mmHg	20:00
Arm occlusion	20:50
Start collection of FBF data	21:00
Baseline	21:00-22:00
Stroop task	22:00-24:00
Recovery	24:00-25:00
Forehead Cold Pressor	25:00-26:00

Recovery	**26:00-27:00**
Release cuff pressure and stop collection of FBF data	27:00
Recovery	**27-32 min**
LBNP/stress protocol	**32-43 min**
Inflate wrist cuff to 180 mmHg	32:00
Arm occlusion	32:50
Start collection of BF data	33:00
Graded ↑ in LBNP to -20 mmHg (-1 mmHg/2 s)	33:15
Stroop task + LBNP	34:00-36:00
Graded ↓ LBNP back to baseline	36:00-37:00
Graded ↑ in LBNP to -20 mm Hg (-1 mmHg/2 s)	37:15
Forehead Cold Pressor + LBNP	38:00-39:00
Recovery (during Graded ↓ LBNP back to baseline)	39:00-40:00
Release cuff pressure and stop collection of FBF data	40:00
Break	**40-50 min**
Stop all data collection	
Remove subject from LBNP chamber	
Prepare subject for $\dot{V}O_{2max}$ test	
Incremental $\dot{V}O_{2max}$ test (cycle ergometer)	**50-65 min**
Monitor subject and finish	**65-80 min**
(recovery BP, HR)	

Appendix IIA Study II Information Sheet

THE PHYSICAL ACTIVITY AND HEALTH RESEARCH UNIT
DE MONTFORT UNIVERSITY, BEDFORD

INFORMATION FOR SUBJECTS

1. *Project Objectives.* To identify risk markers of hypertension in high risk individuals.

2. *Rationale.* Hypertension presents a serious health concern to the worldwide population. The identification of early risk markers to predict the future development of hypertension is therefore an important and ongoing area of research.

3. *Test Procedures.* Testing will involve the application of surface electrodes and electrode band tape to the upper body, a blood pressure cuff on the left arm, wrist, arm cuffs and a mercury strain gauge on the right arm. Subjects will be required to comply with a set dietary intake 24 hrs prior to testing. Also, subjects will be required to provide two urine samples (one in the morning, pre-test, and one post test). Measurements of heart rate, cardiac output, stroke volume, blood pressure and forearm blood flow will be taken. The experimental procedure will involve a 10-min word colour identification task. Subjects will be required to undergo a maximal oxygen uptake test on a bicycle ergometer, lasting approximately 10-min (if not already tested from first study).

4. *Risks and discomforts.* During the experimental session it is anticipated that your heart rate and blood pressure will rise, although not to levels higher than you would commonly experience. The word-colour identification task may induce mild psychological stress. During the maximal exercise test you may feel a certain amount of discomfort in the legs and chest, but this is quite normal.

5. *Inquires.* Questions concerning the procedures and/or rationale used in this study are welcome at any time. All initial inquiries should be directed to the investigator conducting this project (Mark Hamer, The Physical Activity & Health Research Unit: phone 01234 793465), or Dr. Steve Boutcher (research supervisor: phone 01234 793291).

6. *Freedom of consent.* Participation in this project is entirely voluntary. You are free to deny consent before or during the experiment. In the latter case such withdrawal of consent should be made at the time you specify, and not at the end of a particular trial. Your participation and/or withdrawal of consent will not influence your present and/or future involvement with De Montfort University. In the case of student involvement it will not influence grades awarded by the University.

7. *Confidentiality.* All questions, answers, and results of this study will be treated with absolute confidentiality. Subjects will be identified in the resultant manuscripts, reports or publications by the use of subject codes only.

Appendix IIB Diet Sheet and Example of Dietary Analysis

DE MONTFORT UNIVERSITY
THE PHYSICAL ACTIVITY & HEALTH RESEARCH UNIT

DIET AND FLUID INTAKE GUIDELINES

Please adhere to the following guidelines as closely as possible the day before testing. Record food intake on the next page.

Breakfast:
Bowl of porridge/ or bowl of muesli with semi-skimmed/skimmed milk
And
2 slices toast with jam or marmalade (no spread)
And/or
1 piece of fruit

Glass of fruit juice/water

Lunch:
Sandwich or roll (choose from following fillings: chicken, cheese, or egg salad).
And
Yoghurt or fruit

Glass of fruit juice/water

Dinner:
125g Lean meat (chicken or turkey breast)*/or fish (tuna, salmon, cod)*
And
75-100g pasta or rice
And
Vegetables or salad
And
Yoghurt or fruit desert

Glass of fruit juice/water

* Try to grill or bake meat/fish.

Fluid intake
Try to consume a litre of fluid during the day (in addition to that at meal times). This should preferably be water. Please **DO NOT** drink any CAFFEINE DRINKS (eg, coffee, tea, coke, etc) or ALCOHOL.

DIET AND FLUID INTAKE RECORD SHEET

NAME……. *DATE*……

Breakfast:

Lunch:

Dinner:

Additional notes:

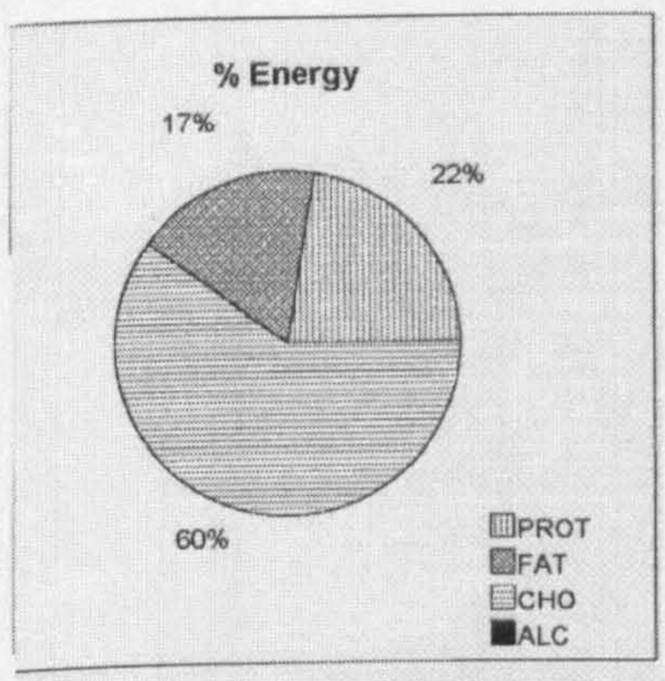
EXAMPLE

30-Nov-2001

NUTRIENT CONTENT

		Amount	RNI	%RNI
Energy	kcal	1571.77	2733.5	57.5%
Protein	g	87.96	55.5	158.5%
Fat, total	g	30.43	(57.63)	52.8%
Polyunsaturates	g	4.43	(10.48)	42.2%
Monounsaturates	g	8.92		
Saturates	g	14.37	(17.46)	82.3%
Carbohydrate	g	252.32	(196.86)	128.2%
Sugars, total	g	113.59		
Starch	g	138.08		
Fibre (Englyst)	g	5.73*	24.0	23.9%
Calcium	mg	1042.18	700.0	148.9%
Phosphorus	mg	1393.83	550.0	253.4%
Magnesium	mg	215.73	300.0	71.9%
Sodium	mg	1392.59	1600.0	87.0%
Potassium	mg	2199.81	3500.0	62.9%
Chloride	mg	2241.52	2500.0	89.7%
Iron	mg	6.25	8.7	71.9%
Zinc	mg	6.76	9.5	71.1%
Copper	mg	0.78	1.2	64.8%
Selenium	µg	75.68*	75.0	100.9%
Iodine	µg	141.07*	140.0	100.8%
Thiamin (B1)	mg	0.91	(0.63)	144.0%
Riboflavin (B2)	mg	1.18	1.3	90.8%
Nicotinic Acid eq	mg	49.05	(10.37)	472.8%
Vitamin B6	mg	1.93	(1.32)	146.0%
Vitamin B12	µg	2.52	1.5	167.9%
Folate	µg	151.97	200.0	76.0%
Vitamin C	mg	81.81	40.0	204.5%
Vitamin A	µg	287.03*	700.0	41.0%
Vitamin D	µg	0.54		
Vitamin E equivalents	mg	3.66*	(1.77)	206.6%
Cholesterol	mg	183.42		
Alcohol	g	0.0*		
Water	g	757.93		

** This is an estimate, as foods providing this amount give incomplete information.*
() Calculated DRV values, shown in parenthesis, are based on levels of other nutrients in the diet.



% energy FAT	17.42
% energy MUFA	5.11
% energy PUFA	2.53
% energy SFA	8.23
Na/K ratio	0.63
Poly/Sat Fat ratio	0.31
Na as Salt in gms	3.54
% energy Carbohydrate	60.2
% energy Starch	32.94
% energy Sugars	27.1
% energy PROTEIN	22.39
% energy ALCOHOL	0.0

Appendix IIC Study II Protocol

STUDY II: EXPERIMENTAL PROTOCOL

Activity	Time
Pre-meeting	**72-48 hrs pre-test**
Provide subjects with dietary guidelines and containers for urine collection	
Dietary control	**24 hrs pre-test**
Subjects to adhere to dietary and fluid intake guidelines	
Baseline urine collection	**8am on day of testing**
Subjects to collect a urine sample immediately after awakening	
Warm–up/check & calibrate equipment	**1 hr pre-test**
(COP, AMLAB, Impedance, Plethysmograph)	
Subject physical screening	**9 am**
Informed consent, PAR-Q, medical questionnaire, STAI, 7-d. PAR	
Outline procedures of experiment and familiarise with Stroop	
Measurement of height, weight, body fat	
Subject preparation	
Standing: fit impedance tape, ECG electrodes	
Subjects required to empty bladder before taking the supine position	
Supine (in LBNP chamber): measure BP (manually)	
attach ECG and impedance leads	
attach Finapress and start (left hand)	
attach forearm strain gauge and occlusion cuffs (right arm positioned at 20°)	
Baseline measurements (supine)	**00-06 min**
Start Collection of COP, AMLAB, BP	00:00
Normal breathing	00:00-03:00
Paced breathing	03:00-06:00
Stress protocol	**06-15 min**
Inflate wrist cuff to 180 mmHg	06:00
Start FBF data collection (baseline)	07:00
(collected for 5 s, every 10 s thereafter)	
Start Stroop	08:00
Stop collection of FBF data	10:00
Inflate wrist cuff to 180 mmHg	15:00
Start FBF collection	16:00
Finish Stroop	18:00
Stop collection of FBF, COP, AMLAB, BP	20:00
Recovery (sitting upright)	**20-35 min**
Post-stress urine collection	**35 min**

freeze urine samples (-20°C) immediately after testing.

Appendix IIIA Study III Information Sheet

THE PHYSICAL ACTIVITY AND HEALTH RESEARCH UNIT
DE MONTFORT UNIVERSITY, BEDFORD

INFORMATION FOR SUBJECTS

1. *Project objectives.* To investigate the effects of acute exercise on cardiovascular responses to mental stress in offspring hypertensives.

2. *Rationale.* Hyper-reactive responses to stress have been linked with the development of hypertension. Thus, it is important to investigate methods of reducing hyper-reactivity to stress in individuals at high risk.

3. *Test procedures.* Testing will involve three separate visits to the laboratory. Firstly, Subjects will be required to undergo a maximal oxygen uptake test on a bicycle ergometer, lasting approximately 10 min (if not already tested from previous studies). The next two sessions will involve performing a 10-min word colour identification task while measurements of heart rate, cardiac output, stroke volume, blood pressure and forearm blood flow are taken. These measures require the application of surface electrodes and electrode band tape to the upper body; a blood pressure monitor attached to a finger of the left hand; a wrist cuff, upper arm cuff and a mercury strain gauge on the right arm. Before one of these sessions subjects will be required to perform 30 min of sub-maximal cycle ergometry exercise. Subjects will be required to comply with a set dietary intake 24 hr prior to each session and testing will be performed after an overnight fast.

4. *Risks and discomforts.* During the testing sessions it is anticipated that your heart rate and blood pressure will rise, although not to levels higher than you would commonly experience. The word-colour identification task may induce mild psychological stress. During the 30-min submaximal exercise session and maximal exercise test you may feel a certain amount of discomfort in the legs and chest, but this is quite normal.

5. *Inquiries.* Questions concerning the procedures and/or rationale used in this study are welcome at any time. All initial inquiries should be directed to the investigator conducting this project (Mark Hamer, The Physical Activity & Health Research Unit: phone 01234 793465), or Dr. Steve Boutcher (supervisor: phone 01234 793291).

6. *Freedom of consent.* Participation in this project is entirely voluntary. You are free to deny consent before or during the experiment. In the latter case such withdrawal of consent should be made at the time you specify, and not at the end of a particular trial. Your participation and/or withdrawal of consent will not influence your present and/or future involvement with De Montfort University. In the case of student involvement it will not influence grades awarded by the University.

7. *Confidentiality.* All questions, answers, and results of this study will be treated with absolute confidentiality. Subjects will be identified in the resultant manuscripts, reports or publications by the use of subject codes only.

Appendix IIIB Study III Protocol

STUDY III: EXPERIMENTAL PROTOCOL

Activity	Time allocated
Day 1: Initial screening (Medical history, informed consent, maximal oxygen uptake test, explanation of protocol and dietary information)	**30 min**
Day 2 or 3:Treatment A (exercise)	**Begin 9 am**
Cycling Ergometry	**0-30 min**
Record pre-exercise body mass	
Set up subject on cycle ergometer, attach HR monitor	
Gentle warm-up (80 W, 60-80 rev.min^{-1})	0-5 min
Adjust intensity to 60% of maximum load (whilst maintaining pedalling)	on 5 min
Collect first gas sample/ record RPE, HR*	9-10 min
Collect second gas sample/ record RPE, HR*	14-15 min
Collect third gas sample/ record RPE, HR*	19-20 min
Collect final gas sample/ record RPE, HR*	24-25 min
Gentle cool-down (50 W, 60-80 rev.min^{-1})	25-30 min
Record post-exercise body mass	
* Maintain HR at 75-85% HR reserve.	
Exercise Recovery Period	**30-63 min**
STAI form	
Preparation of subject with ECG electrodes/ impedance band tape	
Attach strain gauge, arm cuffs, heart sounds, ECG, ICG leads, and Finapres whilst lying on bed. (verify BP manually)	30-55 min
baseline data collection (COP, AMLAB, BP)	begin on 55 min
Normal breathing	55-58 min
Paced breathing	58-61 min
Begin baseline FBF data collection (inflate wrist cuff @ 60 min)	61-63 min
Stress Protocol	**63-73 min**
Begin Stroop	on 63 min
Stop collection of FBF data	on 65 min
Re-start collection of FBF data (inflate wrist cuff @ 70 min)	on 71 min
Stop Stroop	on 73 min
Stress Recovery	**73-78 min**
Stop collection of FBF	75 min
Stop COP, AMLAB, Finapres	78 min
Ask subjects to rate Stroop task on Borg scale	

Day 2 or 3: Treatment B (attention control task)
Repeat protocol for treatment A, except substituting cycling ergometry with a 30-min control attention task to involve dietary analysis and measurement of height, weight, and four site skinfold. Treatments A and B to be administered in a counterbalanced order between subjects, with at least 48 hr recovery between treatments.

Appendix IV Publications

Journal of Human Hypertension (2002) 16, 319–326

www.nature.com/jhh

ORIGINAL ARTICLE

Cardiovascular and renal responses to mental challenge in highly and moderately active males with a family history of hypertension

M Hamer, Y Boutcher and SH Boutcher
The Physical Activity and Health Research Unit, De Montfort University, Bedford, UK

The objective of this study was to compare FBF and renal responses to mental challenge in highly and moderately active males with a family history of hypertension. Normotensive, healthy males with a family history of hypertension ($n = 18$) were recruited into moderately active and highly active groups. Cardiovascular, FBF, and renal responses to a 10-min Stroop mental challenge were measured. Urine was analysed for levels of sodium and potassium pre and post stressor as an indicant of renal blood flow. The results were that the moderately active males demonstrated a significantly higher level of FBF reactivity to mental challenge compared with that of the highly active. Heart rate change and FBF change during the stressor were positively correlated ($r = 0.75$, $P < 0.01$). Both groups, however, demonstrated a similar pattern of sodium excretion to mental challenge. These findings suggest that physical activity level is associated with FBF reactivity but not renal reactivity to mental challenge in offspring hypertensives. That sodium excretion was no different post-stressor in the moderately active group suggests that the exaggerated forearm vasodilatation response was not due to renal vasoconstriction.
Journal of Human Hypertension (2002) **16**, 319–326. DOI: 10.1038/sj/jhh/1001396

Keywords: sodium retention; vascular reactivity; physical activity; familial hypertension; mental stress

Introduction

A critical factor in the development of hypertension is the failure of the kidneys to maintain blood pressure within normal limits by excreting sufficient salt and water.[1] Exercise training is known to be an effective non-pharmacological method to reduce high blood pressure[2] and a number of studies[3,4] have linked exercise antihypertensive effects to renal depressor mechanisms. For example, Kohno *et al*[3] have shown that the renin angiotensin system and sympathetic nervous system were suppressed (significant reductions in plasma renin and noradrenaline activity) after 4 weeks exercise training in hypertensive subjects. A number of studies have also found altered renal haemodynamics both at rest and during mental stress in individuals with a family history of hypertension.[5,6] Furthermore, during stress sodium retention is known to manifest itself particularly in genetically predisposed individuals.[7] Thus, continued exposure to mental stress may be an important contributor to the early development of hypertension in individuals with a genetic predisposition to retain sodium. Although Holmes and Cappo[8] have shown that highly fit offspring hypertensives demonstrate reduced heart rate and blood pressure reactivity to mental challenge compared with less fit offspring hypertensives, the effect of fitness/physical activity level on the renal responses to stress in genetically predisposed individuals appear to be undetermined.

An exaggerated skeletal muscle vasodilatation response to mental stress is also thought to play a key role in the development of hypertension by initiating a vascular re-modelling process.[9] Anderson *et al*[10] suggested that a possible explanation for the enhanced forearm blood flow (FBF) response to stress in offspring hypertensives may have been due to differences in regional blood flow. This hypothesis is supported by a number of researchers[5,6] who have shown that during mental challenge offspring hypertensives have significantly reduced blood flow to the kidney. Activation of the renal α-adrenergic receptors is thought to induce sodium retention through activation of the renin-angiotensin-aldos-

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terone system causing renal constriction (altering glomerular filtration rate) and/or altering the tubular re-absorption of sodium.[11] Thus, if exaggerated FBF reactivity to mental challenge is in part due to a renal vasoconstrictor response then FBF reactors should also display sodium retention. However, no research as yet has examined this relationship.

Thus, given the possible renal depressor effects of regular aerobic exercise, it was hypothesised that highly active offspring hypertensives would demonstrate little or no change in urinary sodium excretion during mental challenge and would also demonstrate reduced FBF reactivity. In contrast it was predicted that moderately active offspring hypertensives would demonstrate sodium retention and exaggerated FBF reactivity to mental challenge.

Methods

Subjects

Eighteen healthy normotensive males with a family history of hypertension were recruited from a student population and from local athletic clubs. The study was approved by a university human ethics committee and all subjects were provided written informed consent before participation.

Subjects were provided with dietary guidelines 24-h prior to testing in order to control for salt intake, which has previously been linked with enhanced cardiovascular reactivity to stress.[12,13] Subjects were also required to abstain from alcohol, caffeine, and rigorous physical activity. Subjects completed a full medical history questionnaire, physical activity readiness questionnaire, the State-Trait Anxiety questionnaire,[14] and were questioned concerning their physical activity levels using the 7-day Physical Activity Recall (PAR).[15] The PAR is a semi-structured interview designed to examine subjects' physical activity during the previous 7 days. Total daily energy expenditure is estimated from the amount of time spent: sleeping (1 MET/h); light activity such as working at a desk (1.5 MET/h); moderate activity such as brisk walking (4 MET/h); hard activity such as playing tennis (6 MET/h); and very hard activity such as running (10 MET/h). Nine males involved with recreational physical activities up to three times per week (eg, football) were recruited for the moderately active group (MOD) whereas nine males who were all aerobic athletes involved with daily aerobic training were recruited for the highly active group (HIGH). Subjects were also asked to provide details of their family history of hypertension which was defined as treated essential hypertension in parents or grandparents. Although subject recall of family history of hypertension has been found to be a reliable method to identify offspring hypertensives in America[16] reliability of the method has not been assessed with UK populations. Thus future research should be directed toward establishing the accuracy of reports of family health history in the UK.

Measures

Impedance cardiology was used (Minnesota Impedance Cardiograph, Model 304B: Instrumentation for Medicine, Greenwich, CN, USA) to estimate stroke volume (SV) using the formula proposed by Kubicek *et al*,[17] and an electrocardiogram (Amlab Physiograph) was used to measure heart rate (HR). Blood pressure (BP) was monitored continuously on a beat-to-beat basis by a Finapres (Model Ohmeda 2300: Ohmeda, Madison, WI, USA). FBF was measured using strain gauge plethysmography.[18] Urine samples were analysed for sodium and potassium content using flame photometry (Gallenkamp FGA-350-L, England). Sodium and potassium measures were corrected for urinary creatinine concentration, and expressed as mmol/mgCr. Urinary creatinine concentration was measured using a spectrophotometer (Model UV–150–02: Shimadzu, Japan) to detect the difference in colour intensity measured at or near 500 nm before and after acidification, which is proportional to creatinine concentration.[19]

Experimental protocol

All testing started at 9 am, after an overnight fast, and was performed in a quiet, air-conditioned laboratory held at a constant room temperature of 24°C.

Baseline: Subjects were instructed to provide a baseline urine sample immediately on awakening on the morning of testing. After 20-min of quiet rest subjects were required to void their bladder. Then an 8-min baseline period of data collection was initiated. During minutes 6–8 baseline FBF was measured.

Mental challenge: This consisted of the Stroop word/colour task.[20] Briefly, subjects were presented with one slide every second on a computer screen for a period of 10 min. Each slide had the name of a colour printed in a contrasting coloured ink for which subjects were requested to identify the colour of the ink, not the name of the colour. Subjects' perceived difficulty of the task, using the Borg 6–20 scale,[21] together with mistakes were recorded. Subjects were encouraged to make as few mistakes as possible. FBF was measured during minutes 0–2 and 8–10 of the mental challenge, but all other cardiovascular variables were measured continuously.

Recovery: Two minutes of recovery in the supine position followed the mental challenge during which all variables were continuously measured. After a further 15-min period of seated upright recovery subjects were instructed to provide another urine sample. Both urine samples were immediately frozen for subsequent analysis.

Maximal oxygen uptake ($\dot{V}O_{2max}$): Finally, subjects were required to undergo an incremental exercise

st to volitional exhaustion in order to measure cardio-respiratory fitness. $\dot{V}O_{2max}$ was assessed using he Douglas bag collection method and gases were nalysed using a zirconia oxide O_2 analyser, and an nfra-red CO_2 analyser. Subjects exercised in the pright position on a stationary electronic ergometer Excalibur Sport. The Netherlands) at a cadence of 0 rpm until volitional exhaustion. The initial load as 30 W for the first 2 min and was increased by W every 2 s thereafter. The end point was achieved hen the subject was unable to continue, and/or eart rate at age-estimated maximum, plateau of xygen consumption, and a respiratory exchange tio greater than 1.10.

ata reduction

pedance cardiograph signals were processed sing ensemble averaging to eradicate artefact from e impedance cardiograph every 25 s, and cardiac ycle timing was verified from heart sounds corded by a phonograph microphone. Each impedace wave was edited through the edit mode of the OP software (COP, Microtronics, Chapel Hill, NC, SA). Cardiac output (CO) was derived from the oduct of SV and HR and total peripheral resistce (TPR) was calculated from MAP/CO.80, pressed as dyne-seconds per cm^{-5}.

An arterial occlusion wrist cuff was continuously lated to suprasystolic pressures (180 mm Hg) dur- FBF measurements, while a venous occlusion per arm cuff was inflated to 50 mm Hg for 5 of ery 15 s providing one blood flow measurement ery 15 s. The gradient of the blood flow wave was presentative of change in forearm volume, which s calibrated for equivalent changes in voltage m the strain gauge. The first second was disrede to avoid errors from movement artefact. A himum of six blood flow measurements was used calculate average FBF for each 2-min block of asures. Forearm vascular resistance (FVR) was bsequently derived by dividing mean arterial ssure (MAP) by FBF.

tistical analysis

peated measures analysis of variance (ANOVA) s employed to identify changes in cardiovascular riables over time and group differences. The thin subject factor comprised of baseline, minutes 2, 4–6, and 8–10 of Stroop, and recovery (2 min). e between subject factor was the two groups ighly and moderately active). A similar analysis s used for FBF and FVR, except no data was colted for minutes 4–6 of Stroop for these variables. A dependent *t*-test was employed to identify anges in urinary variables pre and post stressor thin each group and an independent *t*-test was ed to identify differences in change scores tween groups.

Pearson correlations were performed to investigate the relationship between change in urinary variables and HR change during Stroop, change in urinary variables and FBF change, and HR change and FBF change during Stroop. Also, all subjects were classified into three groups according to the extent of their family history of hypertension. Subjects were put into the highest risk group if they had one parent and one grandparent of hypertensive status, the moderate risk group consisted of offspring with one hypertensive parent, and the low risk group consisted of offspring with a hypertensive grandparent. Correlations were then performed to examine the relationship between risk status with resting blood pressure and reactivity variables.

Results

Physical characteristics and baseline

Subjects' physical characteristics and 24-h dietary intake summary are displayed in Table 1. Three subjects were classified as high risk (a hypertensive parent and grandparent), 11 subjects as moderate risk (a hypertensive parent), and four subjects as low risk (a hypertensive grandparent). The HIGH group displayed significantly higher levels of physical activity and higher $\dot{V}O_{2max}$. Although the HIGH group had higher caloric intake, salt intake was comparatively similar for both groups. Baseline cardiovascular values are shown in Table 2. The HIGH displayed significantly lower resting HR and greater resting SV.

Response to mental challenge

During the Stroop mental challenge there was no significant differences in perceived task difficulty (mean ± SE: 14.6 ± 0.6 *vs* 14.3 ± 0.4) or mistakes (70 ± 12 *vs* 56 ± 14) for the MOD and HIGH groups respectively.

Central cardiovascular responses: For HR there was a significant main effect over time (F (4,

Table 1 Descriptive characteristics and 24-h dietary intake details of moderately active (MOD; $n = 9$) and highly active (HIGH; $n = 9$) subjects with family history of hypertension (mean ± s.e.)

Variable	*MOD*	*HIGH*
Age (yrs)	20.1 ± 0.5	25.3 ± 1.5*
Body mass (kg)	73.1 ± 2.5	75.1 ± 2.5
Height (cm)	179.6 ± 2.5	182.9 ± 3.0
Body fat (%)	14.4 ± 1.0	12.6 ± 1.0
Physical activity (kcal/kg/d)	35.0 ± 0.2	45.0 ± 1.8*
$\dot{V}O_{2max}$ (ml/kg/min)	48.3 ± 1.9	55.3 ± 2.4*
State anxiety	30.7 ± 2.4	30.8 ± 1.5
Calorie consumption (kcal)	1571 ± 121	2002 ± 186
Salt intake (g/100 kcal)	0.28 ± 0.03	0.40 ± 0.05
Total salt intake (g)	4.4 ± 0.5	7.7 ± 0.9*
Total sodium intake (mg)	1724 ± 205	3025 ± 354*

*Significant difference between groups ($P < 0.05$).

Table 2 Response to Stroop mental challenge in moderately active (MOD; $n = 9$) and highly active (HIGH; $n = 9$) males with family history of hypertension (mean ± s.e.)

Variable	*Condition*									
	Baseline		*Stroop (0–2 min)*		*Stroop (4–6 min)*		*Stroop (8–10 min)*		*Recovery*	
	MOD	*HIGH*	*MOD*	*HIGH*	*MOD*	*HIGH*	*MOD*	*HIGH*	*MOD*	*HIGH*
HR (b/min)	65.4 ± 3	49.8 ± 3†	78.4 ± 6	64.6 ± 4	69.3 ± 8	60.5 ± 4	70.4 ± 6	59.2 ± 4	58.6 ± 7	51.5 ± 3
CO (l/min)	6.1 ± 0.5	5.9 ± 0.05	6.1 ± 0.8	6.2 ± 0.5	5.9 ± 0.9	6.3 ± 0.6	6.2 ± 0.7	6.4 ± 0.6	5.5 ± 0.8	6.1 ± 0.6
SV (ml)	92.4 ± 6	119.8 ± 10†	73.2 ± 7	98.0 ± 7	78.6 ± 9	105.5 ± 8	82.5 ± 7	108.9 ± 8	87.5 ± 9	120.0 ± 10
SBP (mm Hg)	122 ± 3	128 ± 4	142 ± 5	142 ± 5	152 ± 6	153 ± 6	151 ± 5	149 ± 6	143 ± 5	141 ± 6
DBP (mm Hg)	62 ± 3	60 ± 3	77 ± 4	73 ± 3	82 ± 4	77 ± 3	80 ± 3	75 ± 3	73 ± 3	69 ± 4
MAP (mm Hg)	81 ± 3	82 ± 5	98 ± 4	95 ± 3	105 ± 4	102 ± 4	103 ± 4	99 ± 4	96 ± 4	92 ± 4
TPR (dyne-s/cm^5)	1132 ± 101	1197 ± 128	1242 ± 99	1296 ± 117	1326 ± 116	1376 ± 122	1273 ± 96	1338 ± 135	1294 ± 124	1325 ± 155
FBF (ml/100 ml/min)	4.5 ± 1	3.6 ± 0.4	9.0 ± 0.8	5.8 ± 0.9*	–	–	7.5 ± 1	5.6 ± 0.7	4.0 ± 0.9	3.8 ± 0.5
FVR (mm Hg/ ml/100 ml/min)	23.2 ± 4	26.5 ± 3	11.4 ± 0.9	19.9 ± 3*	–	–	16.3 ± 2	20.4 ± 3	31.4 ± 5	28.5 ± 5
U-Na (mmol/mgCr)	0.8 ± 0.1	1.4 ± 0.4	–	–	–	–	–	–	1.7 ± 0.3	2.2 ± 0.7
U-K (mmol/mgCr)	0.04 ± 0.004	0.09 ± 0.03	–	–	–	–	–	–	0.12 ± 0.02	0.18 ± 0.02

HR: heart rate; SV: stroke volume; CO: cardiac output; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; TPR: total peripheral resistance; FBF: forearm blood flow; FVR: forearm vascular resistance; U-Na: urinary sodium excretion; U-K: urinary potassium excretion.
*Significant difference in change between groups in comparison with baseline ($P < 0.05$).
†Significant difference in baseline between groups ($P < 0.05$).

64) = 10.79, $P < 0.05$), but no interaction or between subject effects. HR was significantly increased only during the first 2-min of Stroop in comparison with baseline. There was no significant main effect over time within subjects or between subject effects for CO (F (4, 64) = 0.82, $P > 0.05$). There was a significant main effect over time within subjects for SV (F (4, 64) = 13.77, $P < 0.05$), and between subject effects (F (1, 16) = 6.43, $P < 0.05$), but no group interaction over time. SV was significantly reduced during all stages of the Stroop with respect to baseline (see Table 2).

Blood pressure: There was a significant main within subjects effect over time for SBP (F (4, 64) = 41.97, $P < 0.05$), diastolic BP (DBP) (F (4, 64) = 71.01, $P < 0.05$], and MAP (F (4, 64) = 60.95, $P < 0.05$), but no interaction or between subject effects. Systolic BP (SBP), DBP, and MAP were elevated during all stages of Stroop and recovery in comparison to baseline (see Table 2).

Peripheral vascular responses: There was a significant main effect within subjects for TPR (F (4, 64) = 10.53, $P < 0.05$), but no interaction or between subject effects. TPR was significantly elevated during all stages of Stroop and recovery in comparison to baseline. There was a significant main effect (F (3, 48) = 50.75, $P < 0.05$), and interaction (F (3, 48) = 7.3, $P < 0.05$) over time within subjects for FBF. FBF was significantly increased during both the first and last 2 min of Stroop in comparison with baseline. Subsequent analysis revealed that during the first 2 min of Stroop the MOD group displayed a significantly greater increase in FBF compared with that of the HIGH (F (1, 16) = 7.9, $P < 0.05$) (see Figure 1). There was a significant main effect for FVR (F (3, 48) = 20.39, $P < 0.05$), and a trend for an interaction over time. FVR was significantly reduced during both the first and last 2 min of Stroop in comparison with baseline. Also, during the first 2 min of Stroop the MOD group displayed a significantly

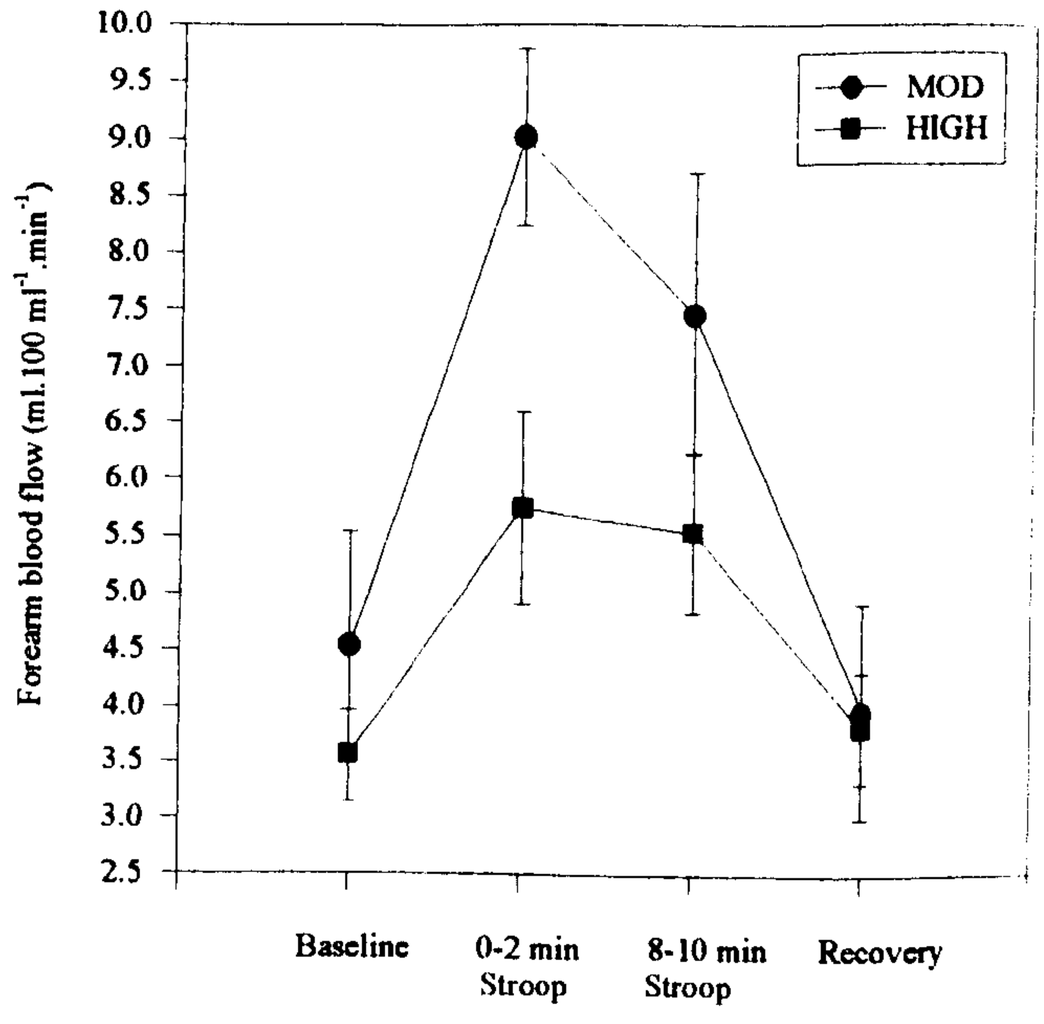
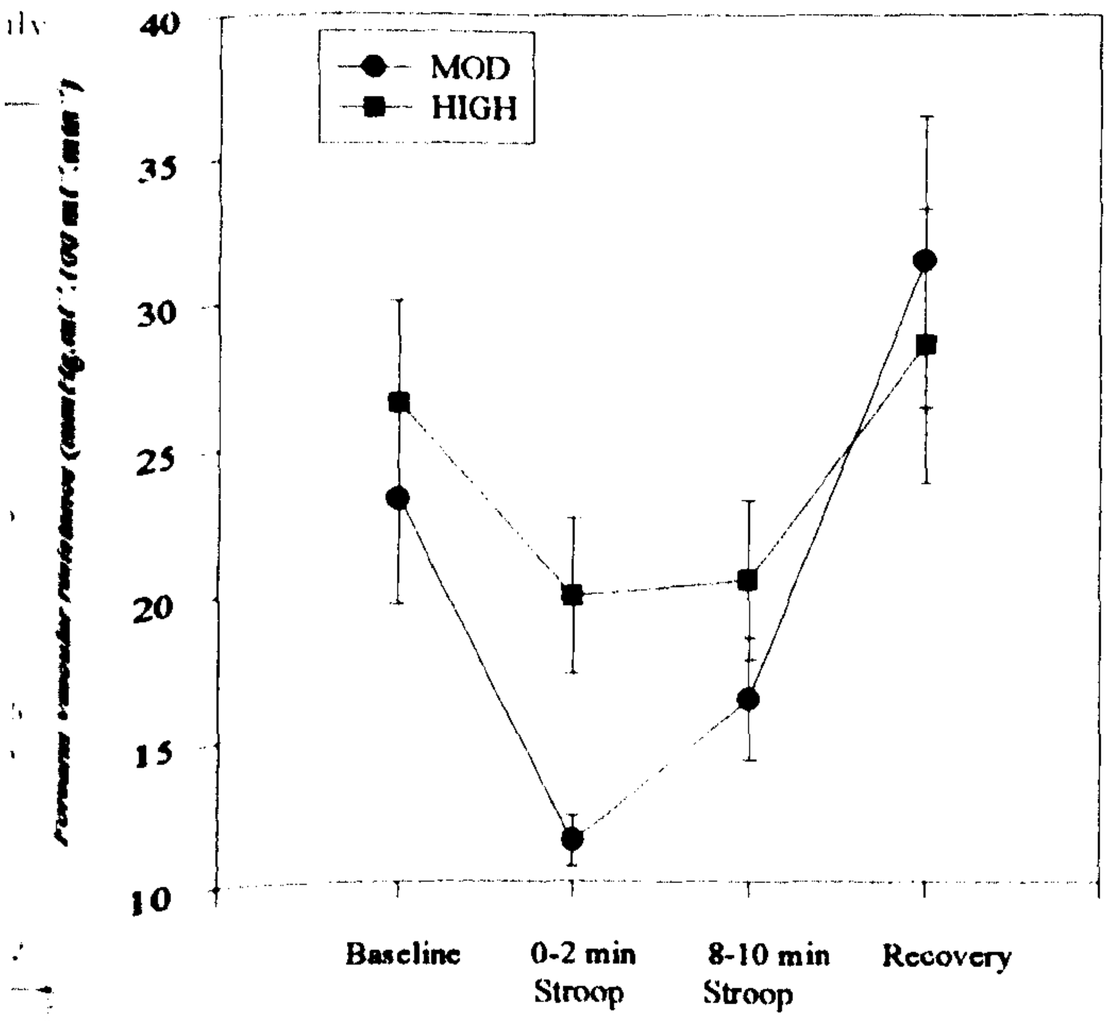


Figure 1 Forearm blood flow response to Stroop mental challenge in highly and moderately active offspring hypertensives.



ure 2 Forearm vascular resistance response to Stroop mental llenge in highly and moderately active offspring hyperten-es.

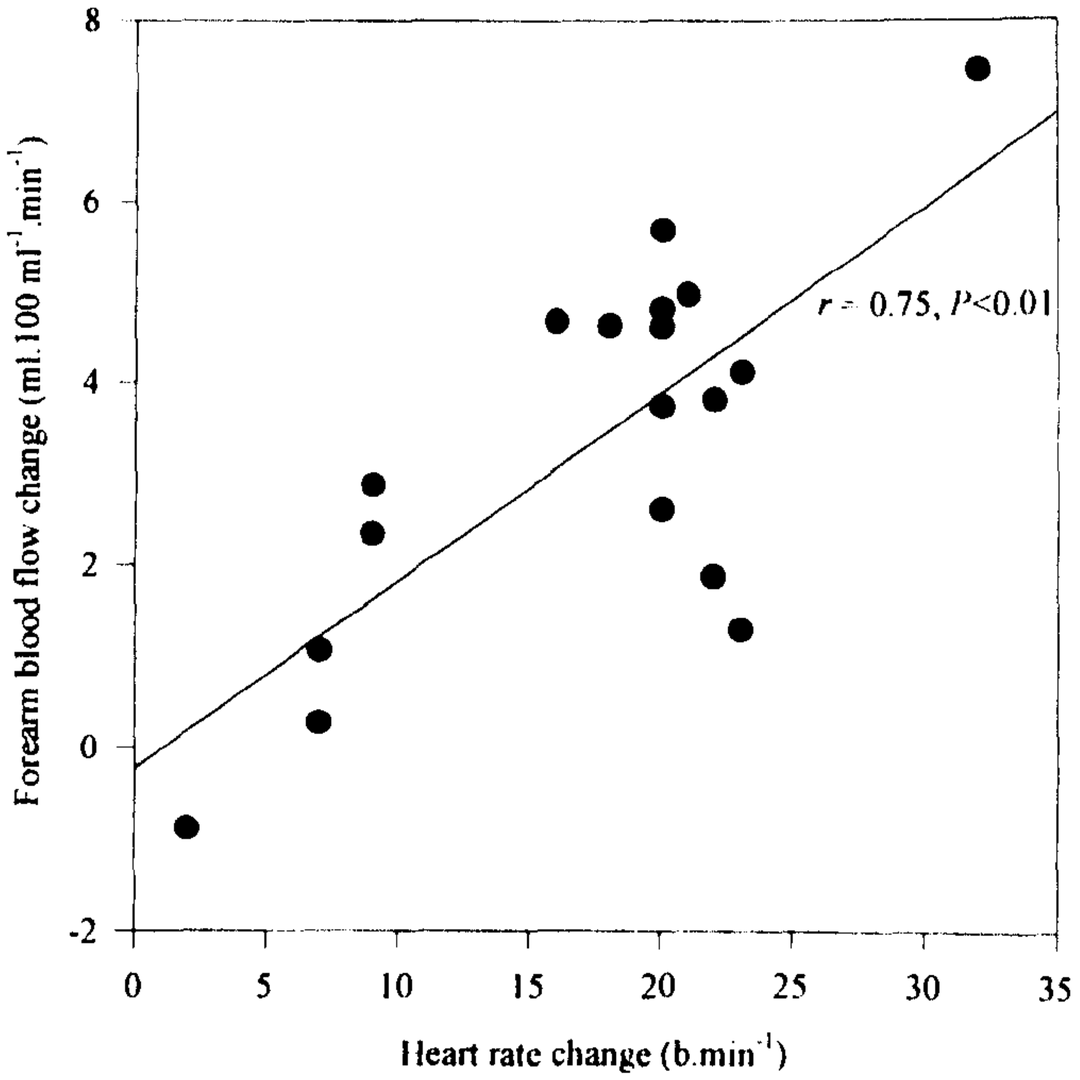


Figure 3 The relationship between change in heart rate and forearm blood flow during the first 2 min of Stroop mental challenge in male offspring hypertensives.

ater reduction in FVR compared with the HIGH $(1, 16) = 9.09$, $P < 0.05$) (see Figure 2 and Table 2).

nal responses: There was a significant increase urinary sodium (t (1, 17) = 3.65, $P < 0.05$) and assium levels (t (1, 17) = 4.77, $P < 0.05$), post ss in comparison with baseline (see Table 2). The nge in sodium and potassium levels from pre to t stressor were however not significantly differ- between groups.

relations

ere was no relationship between urinary sodium nge and HR change ($r = -0.33$, $P > 0.05$) or uri- y potassium change and HR change ($r = -0.24$, > 0.05). Nor was there a relationship between uri- y sodium change and FBF change ($r = -0.09$, > 0.05) or urinary potassium change and FBF nge ($r = -0.11$, $P > 0.05$). There was however a nificant correlation ($r = 0.75$, $P < 0.01$) between change and FBF change during the first 2 min of Stroop mental challenge (see Figure 3).

here was a significant correlation between risk us and both SBP ($r = 0.88$, $P > 0.05$) and DBP nge to the Stroop ($r = 0.75$, $P > 0.05$) only in the D group. That is, individuals with higher risk us demonstrated greater changes in BP during oop.

cussion

e purpose of the study was to investigate the ociation between physical activity level and car- vascular and renal responses to mental challenge in offspring hypertensives. If exaggerated FBF during mental challenge was due to a renal vasoconstrictor response then it was predicted that high forearm vascular responsiveness should be characterised by sodium retention. Because the moderately active offspring hypertensives displayed greater FBF reactivity to mental challenge it was expected that this group would also retain sodium. However, this was not the case, despite similar CO and BP responses to mental challenge between the high (MOD group) and low FBF reactors (HIGH group). These results suggest there may be regional blood flow differences in other vascular beds. It is possible that all of the major skeletal muscle vascular beds do not react in a similar way to mental challenge. However, Halliwell[22] has suggested there is a strong correlation between the skeletal muscle vascular reactivity of the forearm and calf. Research using spontaneously hypertensive rats (SHR) and normotensive controls (Wistar-Kyoto (WKY)) has shown that although both strains demonstrate similar BP changes to the defence response, regional blood flow changes are different.[23] Specifically, SHR demonstrated increases in mesenteric vascular resistance that appeared to be offset by more pronounced decreases in hindquarter vascular resistance (increased skeletal muscle vasodilatation).

Haemodynamic effects

During the mental challenge a number a haemodynamic changes occurred for both groups that were characteristic of the defence response. These changes included significant increases in HR, BP,

TPR, and skeletal muscle vasodilatation. BP and FBF were significantly elevated throughout the mental challenge whilst HR was only significantly elevated at the beginning. This suggests that peripheral compared with central haemodynamic response may play a more important role in the defence reaction brought about by continued exposure to mental challenge.

Vascular stress-reactivity mechanism

The finding that HR change and FBF change during mental challenge were significantly correlated supports the notion that one common mechanism underlies cardiac and vascular reactivity. It is plausible that this mechanism may involve sympathetic activation of β1- and β2-adrenergic receptors that produce increased HR and skeletal muscle vasodilatation. This notion is supported by the findings of Miller and Ditto[24] that strongly implicate the sympathetic nervous system in the exaggerated cardiovascular response to stress in offspring hypertensives. Their study employed the use of selective pharmacological blockade (a β1-adrenergic blocker and an α1-adrenergic blocker). HR and FBF response between offspring hypertensives and controls during a 1-h active coping psychological stressor under a placebo and two drug conditions was compared. Under the placebo condition the offspring hypertensives demonstrated exaggerated HR and FBF responses to the stressor. Under the β1-adrenergic blocking condition only differences in HR response were abolished. These results suggest that the initial forearm vasodilatation response to stress and the reductions in forearm vascular resistance are reinforced by β2-adrenergic or cholinergic activity. Furthermore, Halliwell *et al*[25] examined skeletal muscle vasodilatation to mental stress in order to determine the extent to which this response was due to sympathetic withdrawal, active neurogenic vasodilatation, or β-adrenergically mediated vasodilatation. Firstly, they found that muscle sympathetic nerve activity to the forearm was inhibited during mental stress (a 2.5-min Stroop task), suggesting that sympathetic vasoconstrictor withdrawal may contribute to the vasodilatation response. However, the vasodilatation during mental stress continued to occur after both selective blockade of α-adrenergic neurotransmission and local anaesthetic blockade of the stellate ganglion. Also, after administration of propanolol (a β-2 blocker) the vasodilatation response to stress was reduced but not completely abolished. Thus, the authors concluded that sympathetic withdrawal, through a reduction in discharge of noradrenaline from the autonomic nervous system, may mediate the initial vasodilatation. Then the response could be further augmented by both adrenaline, secreted from the adrenal gland, acting via β-adrenergic receptors and activation of local mechanisms that release nitric oxide. Such local mechanisms may include the release of acetylcholine from selected endothelial cells stimulated mechanically by increases in blood flow and rises in arterial BP. The locally released acetylcholine is then thought to act on muscarinic receptors and cause nitric oxide release producing vasodilatation.[26]

Exercise-induced reactivity lowering mechanism

Differences in sympathetic withdrawal, β-adrenergic receptor activation, and/or local vasodilatation mechanisms may explain the difference in FBF reactivity to mental challenge between the moderately and highly active offspring hypertensives. However, it is interesting to note that the forearm vasodilatation response was only significantly different between the groups during the initial first 2 min of the mental challenge. This therefore suggests that differences in the response are more likely to be due to sympathetic withdrawal and β-adrenergic mechanisms because local mechanisms are thought to sustain rather than initiate the response. Results from animal studies have shown that after an acute bout of exercise vascular responsiveness was reduced.[27] Using vasoactive agonists infused into the hindlimb of the conscious rabbit, blood flow responses in the isolated hindlimb were markedly reduced following a bout of treadmill exercise to exhaustion. The authors suggested that this may be due to an exercise-induced down regulation of α and/or β-adrenergic receptors. Furthermore, longitudinal studies[4,28,29] have consistently shown that endurance training reduces resting plasma catecholamine concentration. However, because plasma catecholamine levels represent a measure of average sympathetic neural activity, it is difficult to determine whether central, peripheral, or local mechanisms are primarily or secondarily responsible for the changes. Studies employing methods to measure post-ganglionic sympathetic nerve traffic have suggested that the reduction in sympathetic nervous activity from training originates from a central effect of training.[30]

Therefore, the mechanism responsible for a possible exercise-induced vascular stress reactivity lowering effect may be a downregulation of α-receptors reducing the sympathetic withdrawal response. Also a down regulation of β-adrenergic receptors and/or reductions in sympatho-adrenal activation, reducing adrenaline discharge, and thus reducing the β-adrenergic vasodilatation response could occur. Evidence from the SHR model[23] suggests that the enhanced β-2 adrenergic vasodilatation in the SHR during the defence response is due to an increased release of adrenaline as opposed to greater receptor sensitivity. Research studying plasma catecholamine concentration during mental stress in human offspring hypertensives also supports findings from the SHR study. Falkner *et al*[31] have shown that post-stress plasma catecholamines were higher in offspring hypertensives compared with controls.

Also, Horikoshi *et al*[32] found that offspring hypertensives who were high BP responders to mental stress also displayed significantly higher levels of adrenaline throughout mental stress.

Renal responses to stress

That sodium retention was not displayed in the offspring hypertensives in the present study is in contrast with the findings of Light *et al*[7] who found that out of a sample of 13 offspring hypertensives, those who displayed high HR reactivity to mental challenge ($n = 7$) had reductions in sodium and water excretion of 27% and 35% respectively. This was in comparison with the low HR reactors with family history of hypertension ($n = 6$) who demonstrated increases in sodium and fluid excretion of 4%, and individuals with no family history demonstrating 1% increases. Given the high correlation between HR reactivity and sodium retention ($r = 0.64$, < 0.05) in the Light *et al*[7] study, a common mediation by the sympathetic nervous system for the cardiac and renal reactivity responses was suggested. This relationship has also been shown in the HR where renal denervation reduces sodium retention and delays the pathogenic process.[33] There are number of reasons to explain why subjects in the present study reacted in a similar manner to the low ak group in the Light study (ie, displayed sodium cretion responses to stress), despite the presence significant cardiac reactivity in the present sub- ts. Firstly, although Light *et al*[7] employed a simi- type of mental stress (cognitive processing task), eir task lasted for a period of 1 h compared with min in the present study. Miller and Ditto[24] demstrated that during an extended 1-h active-coping tessor a pattern of increasing vascular resistance as observed that is thought to be due to increased adrenergic involvement. Thus, extended periods stress may be required to produce renal vasonstriction responses and sodium retention. Secndly, because all subjects in the present study were hysically active, a moderate level of physical tivity may be adequate to reduce a familial tendcy to retain sodium. It should be noted that subcts in the moderately active group were in fact all hysically fit with an average $\dot{V}O_{2max}$ of .88 ml/kg/min. Lastly, in another study that investgated the effect of prolonged isometric exercise on nal excretion of sodium and potassium, there were o differences in this response between offspring ypertensives and controls.[34] Therefore, because dium retention following isometric exercise is en in hypertensive patients, it is possible that the dium retention response to stressors is a conseuence of, rather than a predisposing factor to, ypertension.

Summary

Both the highly and moderately active offspring hypertensives displayed a sodium excretion response to stress. Although neither group demonstrated disturbed renal responses during mental challenge, which has previously been identified as a significant risk marker for hypertension development, the moderately active offspring hypertensives demonstrated an enhanced FBF reactivity response to mental challenge. Repeated episodes of a hyperreactive vascular response to stress has in itself been linked to the development of hypertension through a vascular re-modelling process.[9] Furthermore, that risk index was associated with the SBP response to stress in the moderately active but not highly active group provides further evidence that habitual physical activity is associated with reduction in genetic risk factors of hypertension.

In conclusion, habitual physical activity is associated with reduced vascular reactivity to a laboratory stressor in offspring hypertensives. That differences in renal response to mental challenge between highly and moderately active groups have not been observed suggests that either a moderate level of physical activity may alleviate familial abnormalities in renal functioning, or that physical activity level is not associated with renal responses to stress in offspring hypertensives.

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