ISOMETRIC HANDGRIP EXERCISE, AORTIC DISTENSIBILITY, AND CARDIOVASCULAR RESPONSES

EFFECTS OF 8-WEEK ISOMETRIC HANDGRIP EXERCISE ON AORTIC DISTENSIBILITY AND CENTRAL CARDIOVASCULAR RESPONSES.

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Abstract

Recent evidence suggests that isometric handgrip training improves resting arterial blood pressure (BP) in normotensive and hypertensive individuals, however the mechanisms remain elusive. The purposes of the current investigation were to replicate the finding that 8 weeks of isometric handgrip training (IHG) improve resting BP in persons medicated for hypertension, to determine if training could improve aortic stiffness and to examine the acute cardiovascular response to IHG. Seventeen participants were recruited and familiarized with the laboratory and techniques used. Training consisted of 8 weeks of thrice weekly IHG training sessions using a pre-programmed handgrip dynamometer (4, 2-minute contractions separated by 4 minutes rest). Measurements of resting ABP (assessed by automated oscillometry), aortic stiffness (assessed by simultaneous ultrasound and applanation tonometry), and the acute cardiovascular response (heart rate, blood pressure, rate-pressure product, and cardiac output) were made at baseline and following 8 weeks of IHG training.

Following training, there were no differences observed in resting systolic or diastolic systolic blood pressure, resting heart rate or cardiac output. Furthermore, handgrip training did not improve aortic distensibility or reduce stiffness index. The acute responses of heart rate, blood pressure, rate pressure product and cardiac output were not altered with training. In response to an acute bout of IHG there were significant increases seen in heart rate (55±2 to 65±3 BPM, $p<0.01$), blood pressure (systolic: 137.2±3.7 to 157.1±7.3; diastolic: 77.8±3.4 to 92.2±4.8 mmHg, $p<0.01$) and rate-pressure product (7369.4±302.0 to 10159.0±666.6 beats×mmHg/min). Thus isometric handgrip training is

a safe modality which does not appear to alter the stiffness of the proximal aorta or generate a significant cardiovascular strain in the acute phase.

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List of Abbreviations

American College of Sports Medicine	ACSM
Antidiuretic hormone	ADH
Angiotensin coverting enzyme	ACE
Aortic root diameter	ARD
Blood pressure	BP
Brightness mode	B-mode
Cardiac output	$\dot{Q}$
Diastolic blood pressure	DBP
Hypertension	HTN
Isometric handgrip training	IHG
Joint National Committee	JNC
Maximum voluntary contraction	MVC
Mean arterial pressure	MAP
Millimeters of mercury	mmHg
Pulse pressure	PP
Pulse-wave velocity	PWV
Renin-angiotensin-aldosterone system	RAAS
Systolic blood pressure	SBP
Sympathetic nerve activity	SNA
Sympathetic nervous system	SNS
Total peripheral resistance	TPR
World Health Organization	WHO

1.0 Introduction and Hypotheses

1.1 Introduction

Elevated and high blood pressure are important determinants in the development of all forms of cardiovascular disease. Hypertension causes approximately 60% of all cerebrovascular disease and 49% of all ischemic heart disease (World Health Organization, 2002). Results from a meta-analysis of large prospective studies demonstrated that even small increases in blood pressure can result in large increases in the risk of developing cardiovascular disease (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). Furthermore the lifetime risk of developing hypertension in both men and women is approximately 90% (Vasan et al., 2002). This clearly demonstrates that hypertension is a major and growing concern. While drug treatments are effective at reducing blood pressure, intensive treatment is often required using multiple drug treatments and adherence to treatment regimens is not always maintained (Lewington et al., 2002; Chobanian et al., 2003).

The effectiveness of physical activity at managing and treating hypertension is well accepted among researchers. Both aerobic (Whelton, Chin, Xin, & He, 2002b) and resistance (Kelley & Kelley, 2000) training are effective at reducing resting arterial blood pressure. In a position statement released from the American College of Sports Medicine, both aerobic and resistance training are cited as integral parts of treatment and prevention of hypertension (Pescatello et al., 2004).

Recent work from our laboratory (Taylor, McCartney, Kamath, & Wiley, 2003; McGowan et al., 2005b) and others (Wiley, Dunn, Cox, Hueppchen, & Scott, 1992; Ray & Carrasco, 2000) have demonstrated that isometric handgrip training has the ability to

reduce resting arterial blood pressure. However, the mechanisms associated with these reductions in arterial blood pressure are not well understood. Furthermore, the acute cardiovascular response, a potential stimulus for the training induced reductions, has not been evaluated.

In addition to having a beneficial impact on resting arterial blood pressure, aerobic exercise also appears to improve arterial stiffness. Several studies have documented reductions in arterial stiffness in young healthy individuals (Cameron & Dart, 1994), in older individuals (Tanaka et al., 2000) and in patients with coronary artery disease (Edwards, Schofield, Magyari, Nichols, & Braith, 2004), while the effectiveness in non-medicated patients with isolated systolic hypertension remains questionable (Ferrier et al., 2001). Early reports on resistance training suggest that this form of exercise may exacerbate arterial stiffening (Bertovic et al., 1999; Miyachi et al., 2004); on the other hand, a recent study from our laboratory did not find increases in arterial stiffness with resistance-type exercise (Rakobowchuk et al., 2005). One early report from our laboratory demonstrated the isometric handgrip training can improve carotid artery distensibility (Visocchi et al., 2004), but the effectiveness of handgrip training at improving central artery distensibility needs to be confirmed.

We hypothesize that a session of IHG will result in acute increases in heart rate, blood pressure, and cardiac output. Furthermore, we hypothesize that 8 weeks of unilateral isometric handgrip exercise will result in: 1) lower resting systolic but not diastolic blood pressure; 2) no changes in resting heart rate or cardiac output; 3) improvements in aortic stiffness; 4) diminished acute responses in heart rate, blood pressure and cardiac output.

1.2 Summary and Purpose

Previous literature indicates that isometric handgrip training lowers blood pressure in both people with high-normal blood pressure and medicated hypertensives however the mechanisms have yet to be determined (Wiley et al., 1992; Taylor et al., 2003). The goal of the current investigation was to examine the mechanistic basis of the previously observed blood pressure reductions with IHG training. In order to accomplish this the purposes were: to replicate the blood pressure reduction seen in previous studies adding to the growing body of evidence that isometric handgrip training results in reductions in arterial blood pressure; to determine if unilateral handgrip training improves aortic distensibility; to identify the acute cardiovascular responses to a single bout of isometric handgrip training and to determine if these responses were altered by 8 weeks of training.

2.0 Review of the Literature

2.1 Epidemiology of Hypertension

High blood pressure (BP) or hypertension remains an important risk factor for the development of cardiovascular disease. Globally the burden of hypertension is estimated to cause 7.1 million deaths annually, which is approximately 13% of total deaths world wide (World Health Organization, 2002). Higher than optimal blood pressure (systolic blood pressure >115mmHg) contributes to 62% of all cerebrovascular disease and 49% of all ischemic heart disease (IHD) with little variation between sex (World Health Organization, 2002). Data from Statistics Canada indicated that in the 2001, 3.25 million Canadians were diagnosed with high blood pressure (Statistics Canada, 2005a). Furthermore, Canadian data indicate that in 1999, there were approximately 15 000 deaths from cerebrovascular disease and 42 000 from ischemic heart disease (Statistics Canada, 2005b). Thus, in Canada, elevated blood pressure causes 30 000 deaths; this number may seem small, but it does not include the role of high blood pressure in indirect causes of death. The results of Lewington *et al.* (2002), illustrated that there is a strong and direct relation between stroke and IHD mo`rtality and blood pressure. From blood pressures as low as 120/70 upwards there is linear relationship over 4 different decades of life (50-59, 60-69, 70-79, 80-89) to the risk of mortality from stroke and IHD (Lewington et al., 2002). The association between blood pressure and risk of mortality is also existent for other forms of vascular disease resulting in death (Lewington et al., 2002).

The current definition of hypertension (HTN) is a classification from the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC). The current definition of HTN is a resting systolic blood pressure (SBP)

≥ 140 mmHg, and/or a resting diastolic blood pressure (DBP) ≥ 90 mmHg. This classification system introduces the new category of pre-hypertension, a blood pressure range from 120-139/80-89, and normal blood pressure is defined as <120/80 (Chobanian et al., 2003). To be classified as hypertensive an individual must meet the blood pressure criteria on more than one occasion, using an average of 2 or more blood pressures per occasion (Chobanian et al., 2003; Kaplan, Mendis, Poulter, & Whiteworth, 2003; Whitworth & World Health Organization International Society of Hypertension Writing Group, 2003).

Data from the Framingham Heart Study illustrated that the lifetime risk of developing HTN in middle aged individuals is 90% (Vasan et al., 2002). Vasan et al., further found that 85% of their study population of 1298 participants all free of hypertension at the onset of study developed HTN within their 25 year follow-up period, and 60% of both men and women received some form of blood-pressure lowering drugs during this time period (Vasan et al., 2002). Additional data from the Framingham heart study illustrated the likelihood of making the transition from a non-hypertensive state to a hypertensive state. Vasan and colleagues (2001) demonstrated that individuals in all non-hypertensive categories (optimum < 120/80, normal 120-129/80-84, or high normal 130-139/85-89[1]) were at some risk of moving up to the hypertension category (Vasan, Larson, Leip, Kannel, & Levy, 2001). For example, individuals in the optimal BP category had a 4-year rate of 5.3% of developing hypertension whereas those in the high-normal category had a 37.3% incidence rate over 4 years of follow-up. Overall, individuals in the normal and high-normal categories were 2 – 4 fold and a 5 – 12 fold more likely to develop hypertension respectively, with no differences seen between sexes (Vasan et al.,

[1] This classification was based on the results of the JNC VI.

2001). These are important statistics as for every 20 mmHg increase in SBP or 10 mmHg increase in DBP there is a doubling of the risk of ischemic heart disease and stroke (Lewington et al., 2002).

2.2 Regulation of blood pressure

The basic principal of blood pressure regulation is quite simple: mean pressure is the product of flow and resistance in the system. Mean arterial blood pressure (MAP) in its simplicity is the product of cardiac output ($\dot{Q}$) and total peripheral resistance (TPR). The complexity of blood pressure is highlighted by the multiple control mechanisms that underlie the acute and chronic regulation of the various determinants of $\dot{Q}$ and TPR (Guyton & Hall, 1996; Bakris & Mensah, 2002).

2.2.1 Acute blood pressure regulation

Acute pressure regulation is mediated by the baroreceptor system, chemoreceptor system, vagus and glossopharangeal nerves, and the central vasomotor centre of the brain (Dampney et al., 2002; Bakris et al., 2002). The barorecepters are located primarily in the aortic arch and in the walls of the internal carotid arteries (Kirchheim, 1976; Guyton et al., 1996). These mechanoreceptors are stimulated by alterations in stretch of the artery caused by alterations in pressure, and they function from within the blood pressure range of 50 – 150 mmHg (Kirchheim, 1976). Once stimulated (via an increase in MAP) the baroreceptors send afferent signals to the nucleus tractus solitarius which projects further to the ventrolateral portion of the medulla, thereby inhibiting the vasoconstrictor action of the medulla and activating the vagus nerve. Stimulation of the vagus nerve creates a two branched response, 1-vasodilation in the arterial and venous system (reduction in TPR) and 2- reduction in heart rate and contractility via increased parasympathetic nervous system innervation (reduction in $\dot{Q}$). These two factors lead to a reduction in MAP. If there is a lack of stimulation of the baroreceptors the reverse occurs. A reduction in stimulation increases heart rate and contractility (increase in sympathetic nervous system

activity, and parasympathetic withdrawal). Furthermore, there is vasoconstriction in the arterial and venous systems to cause an increase in MAP mediated by direct innervation and via norepinepherine. Acutely this system acts to maintain MAP at around 100 mmHg (Guyton et al., 1996; Dampney et al., 2002; Bakris et al., 2002).

The chemoreceptors are similar to baroreceptors with respect to acute blood pressure regulation; however, they are sensitive to the acute changes in oxygen and carbon dioxide concentrations (Guyton et al., 1996; Bakris et al., 2002). Chemoreceptors are located in the carotid arteries and in the aorta. The end termination of the chemoreceptors is in the vasomotor section of the medulla. When there is a reduction in blood pressure that results in reduced blood flow to the chemoreceptors, they become activated because of the reduction in oxygen and increase in carbon dioxide and hydrogen ions. When there is a reduction in blood flow, the chemoreceptors exert their influence by exciting the vasomotor centre, specifically the rostral ventrolateral medulla, causing vasoconstriction and increased heart rate and contractility (Guyton et al., 1996; Dampney et al., 2002).

2.2.2 Long-term blood pressure regulation

Long-term blood pressure regulation involves several systems including the renin-angiotensin-aldosterone system (RAAS), antidiuretic hormone, renal juxtaglomerular apparatus, and pressure natiuresis and diuresis (Bakris et al., 2002). These systems rely on an interaction between hormones and the sympathetic nervous system (Dampney et al., 2002). In response to a reduction in BP, renin is released via the afferent arteriole baroreceptor mechanisms and via an increase in the activity level of the renal sympathetic nerve activity. Renin is an enzyme whose function is to convert angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II via the enzyme angiotensin converting enzyme (ACE). ACE is produced primarily in the lungs, but there is local production on the vascular endothelial cells (Guyton et al., 1996; Weir & Dzau, 1999; Bakris et al., 2002). Angiotensin II then exerts its influence acutely (minutes to hours) and over a more sustained period of time. Acutely, angiotensin II acts as a potent vasoconstrictor. The more sustained effects of angiotensin II are via direct stimulation of the sympathetic nervous system, kidneys and the adrenal glands, the latter of which cause sodium and water reabsorption, and activation and release of aldosterone (which acts directly on the kidney) (Guyton et al., 1996). Angiotensin II also exerts local effects on on the heart, kidney (directly causing sodium and water reabsorption), and blood vessels and is responsible for local effects such as increases in osmotic pressure, and vascular remodelling (Weir et al., 1999).

Antidiuretic hormone (ADH) also plays a role in regulating blood pressure. ADH is formed in the hypothalamus and released from the posterior pituitary in response to alterations in blood pressure. The primary event leading to the release of ADH is

reduction in MAP. When blood pressure drops and baroreceptor firing is reduced stimulation of the hypothalamus causes the release of ADH from the posterior pituitary (Guyton et al., 1996). Like angiotensin II, ADH functions as a vasoconstrictor and as a mechanism of water conservation (Bakris et al., 2002).

The longest acting regulator of blood pressure is pressure natriuresis and diuresis. This mechanism is important because of its potential efficacy in the treatment of HTN (Bakris et al., 2002). Pressure natriuresis and diuresis are the body's mechanism of excreting water and sodium when MAP is too high or retaining sodium and water when MAP is too low (Bakris et al., 2002). Sodium and water balance are primarily regulated by the renal system through the use of feedback mechanisms which influence renal sympathetic nerve activity (Lohmeier, 2001; Dampney et al., 2002). Changes in TPR and $\dot{Q}$ that are mediated by neural responses to acutely alter MAP do have an influence on chronic blood pressure regulation. Furthermore, alterations in neurohormonal regulatory levels (see above) can alter the activity of renal sympathetic nerve activity (Lohmeier, 2001).

There is a high degree of complexity and redundancy in the regulation of blood pressure. Blood pressure regulation is a highly flexible system designed for increases in $\dot{Q}$and TPR to help meet the physiological demands of the body. Most importantly, within the regulatory systems there are sufficient counter-regulatory mechanisms designed to help restore blood pressure to normal levels when metabolic demands return to normal (Bakris et al., 2002). In addition to these complex mechanisms, blood pressure is also regulated locally via sympathetic nerve activity, vasoactive hormones, local endothelial function and the stiffness of the artery (Dampney et al., 2002; Bakris et al., 2002).

2.3 Pathogenesis of hypertension

The exact etiology of hypertension remains unknown. There are many mechanisms responsible for the acute and long-term regulation of blood pressure, and an alteration in the normal functioning of any of the aforementioned mechanisms could potentially result in hypertension. Some of the possible causes of hypertension include genetics, environmental causes, malfunctioning of the RAAS, increases in sympathetic nerve activity, alterations in arterial stiffness, and diseases of the kidney.

The recent advances in genetics have elucidated genetic variants that play a role in the development of HTN (Bakris et al., 2002; Chobanian et al., 2003). According to Bakris and Mensah (2002), 30 – 60% of the variability in blood pressure between individuals can be attributed to genetic factors; however, this figure varies depending on the population. Certain genetic sites that are responsible for angiotensinogen, α and β sub-units on adrenergic receptors, nitric oxide synthase and renal ion channels have been identified as potential polymorphisms partially responsible for the development of HTN (Bakris et al., 2002; Chobanian et al., 2003). To date there remains insufficient data to conclude that genetic variants are solely responsible for hypertension.

Environmental factors also contribute to the development of hypertension and are responsible for at least 20% of the observed variations in blood pressure. The most important population based environmental factors include geography, dietary mineral consumption (sodium, potassium, magnesium, and calcium), physical activity, smoking and environmental tobacco smoke, psychosocial stress and socioeconomic status (Bakris et al., 2002). With respect to individual variations in hypertension occurrence, obesity and metabolic abnormalities such as insulin resistance and dyslipidemia are associated

with the development of hypertension. Currently the increase in obesity in Western societies parallels the incidence of HTN. Age is also a predictor of hypertension with older individuals more likely to develop HTN (Vasan et al., 2001; Vasan et al., 2002; Bakris et al., 2002).

Alterations in sympathetic nervous system (SNS) have frequently been linked to hypertension (Abboud, 1982; Mancia, Grassi, Giannattasio, & Seravalle, 1999; Lohmeier, 2001; Dampney et al., 2002; Bakris et al., 2002). Hypertension is associated with increased sympathetic activity which can have deleterious effects on a variety of blood pressure control mechanisms. When the SNS is activated there is peripheral vasoconstriction mediated by the release of norepinephrine (Bakris et al., 2002). One proposed mechanism for the increase in sympathetic nervous system activity is via elevated concentrations of circulation angiotensin II (Mancia et al., 1999). Within the renal system chronic increases in norepinephrine and renal adrenergic activity have the ability to alter pressure natriuresis, thus altering retention and excretion of water and sodium which cause hypertension (Lohmeier, 2001). Alterations in baroreceptor resetting have also been postulated as a mechanism of the pathogenesis of HTN. When there is chronic elevation in BP, the ability of the baroreceptors to buffer changes in BP and to properly reset becomes impaired (Mancia et al., 1999; Lohmeier, 2001; Bakris et al., 2002). There is data to indicate that when the baroreceptors are malfunctioning, there is no inhibition of the renal sympathetic nerve activity, hence no buffering of angiotensin II (Lohmeier, 2001). Thus, malfunctioning of the sympathetic nervous system and arterial baroreflex system is another potential mechanism in the etiology of HTN.

Alterations in the RAAS have the ability to cause and maintain elevated blood pressure and therefore cause HTN. This system is one of the most important systems in the regulation of blood volume and blood pressure (Bakris et al., 2002). One potential cause of hypertension is an elevated concentration of renin compared to the concentration of sodium in the blood (Bakris et al., 2002). The increase in renin inevitably leads to an increase in angiotensin II which subsequently leads to inappropriate vasoconstriction and increase in sodium and water reabsorption (Bakris et al., 2002). The mechanism of action is the binding of angiotensin II to high affinity type 1 receptors (AT_1). This receptor is responsible for a majority of the known cardiovascular responses to angiotensin II. When angiotensin II binds this receptor vasoconstriction, salt/water retention, growth stimulation and disease progression occur (Weir et al., 1999).

The last major contributor to the development of HTN is the vascular system. Briefly, an increase in arterial stiffness via vascular remodelling or impaired endothelial function would lead to an increase in TPR and hence an increase in blood pressure (Bakris et al., 2002). The role of vascular health specifically, arterial stiffness will be discussed in detail below (see section 2.6).

2.4 Treatment of hypertension

The goal of treatment is to reduce BP to levels less than 140/90 mmHg unless HTN is co-morbid with diabetes or renal disease, in this situation, optimal blood pressure control is less than 130/80 mmHg. The two main methods for blood pressure modulation are lifestyle modification and pharmacotherapy (Chobanian et al., 2003).

Lifestyle modification includes increases in dietary fruits and vegetables, reductions in sodium intake, weight reduction, moderate alcohol consumption and physical activity (Chobanian et al., 2003; Whitworth et al., 2003). Overall these intervention vary in their effectiveness, but can provide reductions in systolic blood pressure from as little as 2 mmHg to as high as 20 mmHg (Chobanian et al., 2003). These reductions are dependent on time intensity, and individual susceptibility. The choice of lifestyle modification opposed to pharmacotherapy is the first treatment option (Chobanian et al., 2003). However, it should be noted that the lifestyle modifications should be maintained throughout the treatment protocol (Chobanian et al., 2003; Whitworth et al., 2003).

Pharmacotherapy is the next treatment option if lifestyle modification does not reduce BP to optimal levels. The choice of antihypertensive medication varies greatly depending on co-morbid conditions, as well as different clinical populations. Regardless, of the antihypertensive drug of choice they are all effective at reducing blood pressure (Neal, MacMahon, & Chapman, 2000). Neal and colleagues of the Blood Pressure Lowering Treatment Trialists' Collaboration (2000) compared the effectiveness of different blood pressure lowering drugs and treatment regimens on blood pressure and certain cardiovascular end-points. This meta-analysis illustrated that all drugs were

equally effective at reducing both systolic and diastolic blood pressure. Differences did arise when more aggressive treatment options were compared to less intense treatment options, or when an active treatment was compared to a placebo (Neal et al., 2000). With respect to cardiovascular outcomes, the effectiveness of pharmacotherapy to reduce the indices of stroke range from 35 – 40%, of myocardial infarction range from 20 – 25% and of heart failure is 50% (Neal et al., 2000). It is likely that the reduction in blood pressure is responsible for the reduction in cardiovascular end-points (Whitworth et al., 2003). Despite the effectiveness of pharmacological therapy there are drawbacks. In the results from the aforementioned meta-analysis, as few as 60% of study participants remained on the assigned treatments during a given study, and on average 25% of the patients changed their medication or withdrew from the study (Neal et al., 2000). This highlights one of the major concerns of pharmacotherapy, adherence. In addition, greater than 66% of all patients being treated for HTN will require two or more drugs from different classes to adequately control their BP (Chobanian et al., 2003; Whitworth et al., 2003). Lastly, there is the associated cost of pharmacotherapy including the financial burden as well as the burden of adverse effects (Whitworth et al., 2003).

Regardless of which approach is taken, there is theoretical data to suggest that even a small reduction in blood pressure is significant in terms of cardiovascular disease incidence and progression. This is a theoretical framework based on a population level intervention/approach. For even small reductions in SBP, there can be a large reduction in the amount of cardiovascular events (World Health Organization, 2002; Whelton et al., 2002a). Specifically, a reduction of 2 mmHg can reduce the mortality of stroke by 6% and coronary heart disease by 4% (Whelton et al., 2002a). Population level strategies

aimed at increasing physical activity and a proper diet can shift the systolic blood pressure curve of the population to more optimal levels (World Health Organization, 2002; Whitworth et al., 2003).

2.5 Effects of exercise on blood pressure

Some early evidence to support exercise as a preventative therapy and treatment modality for hypertension came from the Harvard Alumni Study (Paffenbarger, Jr., Wing, Hyde, & Jung, 1983). Paffenbarger Jr and colleagues (1983) found that individuals who did not engage in vigorous sports were 35% more likely to develop hypertension compared to those who did. Thus, they concluded that vigorous forms of physical activity were associated with lower incidence of hypertension (Paffenbarger, Jr. et al., 1983). Similarly, Blair and colleagues (1984) demonstrated that the risk of hypertension was 1.52 times greater over the twelve year follow-up in sedentary individuals compared to those with the highest exercise capacity even after controlling for age, sex, baseline blood pressure, and baseline body mass index. (Blair, Goodyear, Gibbons, & Cooper, 1984). These early studies demonstrated that there is an inverse relationship between the amount of physical activity and the development of hypertension. Subsequently, this has led to the examination of exercise as a treatment for hypertension.

2.5.1 Chronic effects of exercise on resting blood pressure

2.5.1.1 Effects of aerobic training

To date there have been a number of meta-analyses published on the effects of aerobic training on BP. The advantage of the meta-analysis is that it combines a large number of studies thereby increasing the sample size and the power to detect changes. Halbert and researchers (1997) combined 29 different randomized controlled trials for approximately 1 500 participants who performed training programs for greater than four weeks (Halbert et al., 1997). The results indicated that aerobic training significantly reduced resting SBP by 4.7 mmHg and DBP by 3.1 mmHg. Furthermore, when

participants trained more frequently (7 session/week compared to 3 sessions/week) there was a greater reduction in both systolic and diastolic pressure (Halbert et al., 1997). Similarly, Fagard (2001) concluded that aerobic training reduces SBP and DBP by 3.4 and 2.4 mmHg respectively. This analysis combined 44 trials and included 2 674 participants. In a sub-analysis focusing on the trials that involved hypertensive participants (n=16), there was a more marked reduction in blood pressure of 7.4 mmHg SBP and 5.8 mmHg DBP (Fagard, 2001). Unlike the results of Halbert et al, Fagard found no impact of training frequency (or intensity) on the reduction in BP. Lastly, Whelton and colleagues (2002) completed a meta-analysis of 54 randomized controlled trials and a total of 2 419 patients. They found that with aerobic exercise SBP was reduced by ~3.8 mmHg and DBP was reduced by ~2.6 mmHg (Whelton et al., 2002b). Similar to the results of Fagard, Whelton and colleagues found that when only trials involving hypertensives were included there were greater reductions seen in resting BP; furthermore, there was no impact on frequency intensity or type of training on blood pressure (Whelton et al., 2002b).

In their position stand on exercise and hypertension the American College of Sports Medicine (ACSM) concluded that aerobic exercise can be used as a tool to reduce resting blood pressure. However, they were less conclusive on the effects of aerobic exercise at reducing ambulatory BP because of a limited amount of studies which examined ambulatory BP (Pescatello et al., 2004). The use of aerobic exercise should be incorporated in the early stages of the management of hypertension as there is an overwhelming amount of evidence which indicates that aerobic exercise can reduce blood pressure in a wide variety of populations (Chobanian et al., 2003; Pescatello et al., 2004).

2.5.1.2 Effects of resistance training

While the results of aerobic exercise training demonstrated consistent results, the results of trials which have examined the effectiveness of resistance training on blood pressure have yielded inconsistent results (Pescatello et al., 2004). This is illustrated by two recent meta-analyses which had contradictory results. Kelley and Kelley (2000) provided a detailed analysis of eleven studies which involved 320 participants of which 182 were active participants. The results demonstrated that progressive resistance training reduced resting arterial BP by 3 mmHg (Kelley et al., 2000). Despite this positive finding, Halbert and colleagues (1997) did not find any effect of resistance training on arterial blood pressure. The difference between these two analyses is the number of studies which were included in the analysis. Halbert and colleagues only included three trials, which would explain the lack of significance compared to the results of Kelley and Kelley. In their position stand the ACSM concluded that if people (both hypertensive and normotensive) follow the ACSM's guidelines for resistance training they will reduce their blood pressure (Pescatello et al., 2004). Despite this conclusion, they feel that more studies which examine the effectiveness of resistance training on ambulatory blood pressure are warranted. In their guidelines, the ACSM recommends that resistance training be used to supplement an aerobic-based program.

2.5.1.3 Mechanisms of chronic training induced blood pressure reduction

There are many potential mechanisms through which chronic training can reduce systemic arterial blood pressure. Chronic aerobic training does not typically alter cardiac output because reductions seen in heart rate are typically matched by increases in stroke volume. Therefore, chronic exercise training likely reduces BP via a reduction in TPR. Chronic exercise training may cause reductions in TPR through a variety of mechanisms

including alterations in sympathetic nerve activity, alterations in RAAS, alterations in vascular structure and function and alterations in renal function. Specifically, exercise (primarily aerobic) has been shown to reduce sympathetic nerve activity and improve baroreceptor functioning, improve endothelial function, and improve vascular structure by reducing stiffness (Pescatello et al., 2004).

2.5.2 Acute effects of exercise – post exercise hypotension

During an acute bout of physical activity there is a reflex response in the cardiovascular system to ensure proper perfusion to the exercise tissue. Briefly in response to the onset of physical activity, HR increases via parasympathetic withdrawal and sympathetic activation. The latter is also responsible for vasoconstriction which helps to increase venous return and hence stroke volume and $\dot{Q}$. The metabolic demands of the active muscle are met by an increase in blood flow which is caused by regional vasodilation. Systemic vasoconstriction increases SBP, while DBP does not change or modestly increases. During a bout of resistance training, the increases discussed above are more pronounced as there is also mechanical constriction of the vessels supplying the active muscle driving SBP and DBP up higher than endurance exercise (MacDonald, 2002).

Unlike the chronic training, where alterations are seen following repetitive bouts of physical activity performed over days, weeks or months (i.e. training) there are changes in blood pressure which occur following a single bout of physical activity. Post exercise hypotension (PEH) refers to a reduction in blood pressure below resting values following an acute bout of physical activity (Kenney & Seals, 1993). This decrease in BP varies similar to the way training responses differed (see above), such that the more

hypertensive an individual the larger the PEH response appears to be (Kenney et al., 1993; MacDonald, 2002). In normotensive individuals PEH may reduce BP by 8/9 mmHg, and in hypertensive individuals the PEH elicits a 10/7 mmHg decline in BP (MacDonald, 2002). Exercise type, intensity, and duration do not appear to affect the magnitude or the duration of PEH (Kenney et al., 1993; MacDonald, 2002). The duration of PEH is variable with reductions in BP seen for as little as 1 – 2 hours to a maximum duration of 12 – 16 hours (Kenney et al., 1993; Thompson et al., 2001; Halliwill, 2001; MacDonald, 2002). One likely explanation for the differences in the duration in PEH is the posture (supine vs. seated) and location (in laboratory or out of laboratory) of the BP measurements following an acute exercise bout. With the availability of ambulatory BP monitoring, this allows more representative measures of BP following an acute bout of physical activity as the participants can leave the laboratory setting and investigators can monitor BP during a wide variety of activities of daily living.

While many studies examined the after-effects of exercise on ambulatory BP monitoring, a recent review attempted to consolidate these findings. Pescatello and Kulikowich (2001) examined 23 studies (8 of which examined PEH) where ambulatory BP was used. The results of their analysis demonstrated that the 24 hour SBP and DBP pressures were significantly reduced compared to baseline levels by 3.2 ± 0.8 and 1.8 ± 0.5 mmHg $p \leq 0.05$ respectively. Similar to the previous studies, they found that the hypertensive participants had a greater PEH response than did the normotensive participants, but exercise intensity did not affect the PEH response observed (Pescatello & Kulikowich, 2001).

2.5.2.1 Mechanisms of post exercise hypotension

To date many different regulatory systems have been suggested to contribute to PEH. The mechanisms which many investigators have focused on are alterations in $\dot{Q}$ and TPR as they are the determinants of BP. With respect to $\dot{Q}$ studies have demonstrated inconsistent results, with increases, decreases or no changes in $\dot{Q}$ observed post exercise (Kenney et al., 1993; Halliwill, 2001; MacDonald, 2002). Studies which have examined alterations in TPR have more consistently shown reductions in TPR. The reductions are seen in measures of systemic TPR, and regional TPR in both exercising and non-exercising vascular beds (Kenney et al., 1993; Halliwill, 2001; MacDonald, 2002). The alteration in TPR suggests that PEH is a result of alterations in the vasculature (Halliwill, 2001). One proposed mechanism of PEH is via an alteration in the baroreceptor set point. When this becomes altered to a lower value, there is an attenuation of sympathetic nerve activity (SNA) at a given pressure. The reduction in SNA is seen in most populations but is most pronounced in hypertension, likely because of their elevated levels of SNA seen prior to exercise (Kenney et al., 1993; Halliwill, 2001; MacDonald, 2002). This latter point could help explain why hypertensive subjects have a greater PEH response than normotensive individuals. The alterations in humoral and local vasodilators have not produced consistent results. Halliwell (2001) suggested that there may be increases in vasodilatory substances and an alteration in vascular sensitivity to these substances following exercise. The results from these studies typically are from animals and more studies involving human participants are needed to further understand these mechanisms (Halliwill, 2001; MacDonald, 2002). In addition to the peripheral factors, several studies have suggested that alterations in neural pathways; specifically, an increase in opioids

and an activation of serotinergic pathway, may help reduce sympathetic nerve activity (Kenney et al., 1993; MacDonald, 2002). Overall it appears that there is a complex interaction of both peripheral and central factors that contribute to PEH (MacDonald, 2002).

The implications of PEH can be quite dramatic if one assumes that the duration of the hypotensive effect is around 12 hours. If PEH is sustained for 12 hours then a bout of physical activity every day of the week could continuously sustain blood pressure at lower levels. This assumes that there are no chronic adaptations in blood pressure to physical training; however, as previously discussed, this is not the case. PEH is likely an important mechanism which contributes to the reduction in BP with exercise. More studies which examine the mechanisms of PEH and the interaction of PEH with anti-hypertensive medications are still required. Furthermore, more controlled studies which utilize ambulatory BP monitoring are required to examine the effects of a wide variety of physical activity bouts.

2.5.3 Isometric handgrip training

Early uncontrolled and observational studies have suggested that isometric training has the ability to induce reductions in systemic arterial pressure (Kiveloff & Huber, 1971). The overall efficacy of this training was inconclusive because of the inability to quantify the effort during the exercise session (Kiveloff et al., 1971). A subsequent study by Buck and Donner (1985) compared the incidence of hypertension among jobs requiring different levels of isometric activity. Similar to Kiveloff and Huber, the authors concluded that individuals who preformed moderate to high forms of isometric activity in their jobs were less likely to have hypertension; this relationship remained significant after controlling for smoking status, obesity, and alcohol intake (Buck & Donner, 1985).

To date five studies examining the effects of isometric handgrip training (IHG) have been published. The original work was conducted by Wiley and colleagues (1992) who demonstrated that bi-lateral IHG training reduced resting SBP and DBP in individuals with high normal blood pressure following 8-weeks of training in both a laboratory and workplace setting (Wiley et al., 1992). The training protocol utilized 3 sessions of training per week. Each training session consisted of 4, 2-minute contractions at 30% of each arm's maximal voluntary contraction (MVC) with a 1 minute rest period between contractions of alternating arms. This protocol resulted in a 12.7/14.9 mmHg (SBP/DBP) reduction in resting blood pressure. The reduction in BP was independent of alterations in resting heart rate (Wiley et al., 1992). Building on the results of Wiley, Taylor and colleagues (2003) implemented the same training protocol for 10 weeks in a population of elderly hypertensives (BP $\geq$ 140/85). They found that this protocol resulted

in a significant decrease in SBP in the training group compared to the control group (156±9.4 – 137±7.8 vs 152±7.8 – 144±11.8, and a trend towards a reduction in DBP (Taylor et al., 2003). Most recently, McGowan and colleagues (2005) utilized the bilateral IHG for 8 weeks in a group of individuals who were medicated for hypertension. Similarly to the previous studies they demonstrated that the training elicited a significant reduction in resting SBP 137.0 ± 4.2 to 121.8 ± 4.8 mmHg and a trend toward a reduction in DBP (McGowan et al., 2005b).

Two studies have examined the effects of a uni-lateral IHG protocol on resting blood pressure. Ray and Carrasco (2000) utilized a 5 week training protocol in a group of normotensive individuals. Each training session consisted of 4, 3-minute contractions at 30% MVC separated by 5 minutes of rest. Unlike the previous investigations, this study utilized four training session per week. Following training there was a significant reduction observed in DBP and MAP in the training group, 5 and 4 mmHg respectively. Unlike the previous investigations there was no reduction in resting SBP (Ray et al., 2000). Visocchi and colleagues (2004) had their participants (medicated hypertensives) utilize a slightly different unilateral training protocol compared to Ray and Carrasco. The protocol utilized by Visocchi and colleagues was 4, 2-minute isometric contractions at 30% of MVC interspersed by 4 minutes of rest 3 times per week. Similar to the investigations which utilized bi-lateral training Visocchi and colleagues found a 7.9 mmHg reduction in SBP in medicated hypertensives, and no change in diastolic blood pressure (Visocchi et al., 2004).

The results of these studies demonstrate that IHG has the ability to reduce resting blood pressure in a wide variety of populations. One explanation for the potential

differences in the results of these studies is the differences in training protocol, study duration and population. The potential mechanisms of the reduction in arterial have been suggested but have not been examined conclusively. Taylor and colleagues found that IHG reduced SBP variability and there was a trend toward a reduced HR variability, thus they concluded that IHG may alter autonomic nervous system activity (Taylor et al., 2003). However, Ray and Carrasco demonstrated that the reduction in BP was not mediated by alterations in muscle sympathetic nerve activity (MSNA) (Ray et al., 2000). To further complicate the issue, Sinoway and colleagues (1996) demonstrated 4 weeks of rhythmic fore-arm training increased the MSNA burst count which was not associated with an increase in norepinephrine (Sinoway et al., 1996). These results were similar to those seen in normotensive individuals who trained using a repeated forearm contraction at 30% of MVC (30 contractions per minute) until fatigue, followed by a second bout of this forearm exercise (Somers, Leo, Shields, Clary, & Mark, 1992). Despite no reductions in resting HR or BP, the investigators demonstrated an altered sympathetic nerve response to training (Somers et al., 1992). McGowan and colleagues (2005) demonstrated that bi-lateral IHG improves endothelial function; however, a subsequent study in normotensives found that uni-lateral IHG reduces blood pressure but was independent of changes in endothelial function (McGowan, Levy, McCartney, & Macdonald, 2005a). In support of improved arterial compliance as a mechanism of arterial blood pressure reduction, Visocchi and colleagues (2004) demonstrated that unilateral training improves carotid artery distensibility 0.1105 $mmHg^{-1} \times 10^{-2} \pm 0.0093$ to 0.1669 $mmHg^{-1} \times 10^{-2} \pm 0.0221$. To date, no study has examined the post exercise hypotensive effect of IHG.

The results of these studies are suggestive that a potential mechanism of altered arterial blood pressure following training is a result of alteration in sympathetic nerve activity (Somers et al., 1992; Sinoway et al., 1996). A possible explanation for the alteration in sympathetic tone could be the result of improved baroreflex sensitivity because of an improvement in central artery stiffness. Monahan *et al.* (2001) demonstrated that physical activity may attenuate the decline in neural and mechanical components of cardiovagal reflex control (Monahan, Tanaka, Dinenno, & Seals, 2001). Thus, improvements in aortic stiffness could contribute to enhanced baroreflex control of blood pressure, thus attenuating sympathetic nerve activity.

2.5.4 Cardiovascular response to isometric handgrip exercise

To date only the studies conducted by Wiley et al (1992) and Ray Carrasco (2000) examined the cardiovascular response to a bout of isometric handgrip exercise. Wiley and colleagues examined the change from rest in systolic and diastolic pressure in the final 30 seconds of the first contraction. They found a 16.8 ± 1.01 mmHg increase in SBP and DBP increased by 15.9 ± 0.90 mmHg during this time period (Wiley et al., 1992). Similarly, Ray and Carrasco also used the second minute of IHG and as an indicator of the cardiovascular response to this exercise. They found significant increases in heart rate (~9 beats/minute), and mean arterial pressure (~18 mmHg), however there was no training effect observed. While these studies give an insight into the cardiovascular response to a two-minute bout of isometric handgrip training, the majority of the training response has not been described.

2.6 Vascular stiffness

2.6.1 Vascular physiology

The arterial system acts as a conduit system between the heart and the periphery. Thereby blood must be delivered with only a minimal drop in mean pressure to ensure adequate perfusion. The second function of the arterial system is to act as a cushion. This cushioning function serves to transfer the pulsatile output from the left ventricle into a laminar flow to ensure continuous flow through arterioles and capillaries (O'Rourke, 1990).

The arteries are made of 3 concentric layers, each comprised of different structural components. The outer most layer is the adventia which is comprised primarily of collagen and some elastin. The middle layer is the media, this is the thickest of all layers and is comprised of vascular smooth muscle, elastin and some collagen fibers. The inner most layer is the intima layer. This layer contains the endothelial cells which face the lumen of the vessel. The basal membrane that they are connected to is comprised primarily of elastin tissues. These layers all contribute to the ability of the artery to expand and contract to serve as the cushion and to prevent abnormal flow (Izzo, Jr., 2004; Zieman, Melenovsky, & Kass, 2005). During higher pressure of systole, there is primarily loading of the collagen fiber. During the lower pressure loads of diastole, the contractile elastic units (elastin and smooth muscle) are loaded (Izzo, Jr., 2004). More specifically, between 40 – 50% of the stroke volume is directly transferred through the aorta and central arteries to the periphery. The remainder is stored in the aorta which has distended greatly to accommodate the load. During diastole, the aorta (and other central arteries) recoil and further push the blood through the arteries, this helps contribute to the

laminar flow (London, 2005). During this time of recoil a portion of the wave (pressure of blood) is pushed backward towards the heart. This reflected wave meets the next wave and there is some pressure summation (Izzo, Jr. & Shykoff, 2001). The reflected wave is an important determinant of left ventricular load and myocardial perfusion (O'Rourke, 1990; Kass, 2002).

The ability of the arterial system to expand and contract in response to changes in pressure is known as arterial distensibility. A more distensible artery can accommodate larger changes in pressure (or volume). The central elastic arteries account for greater than 80% of the overall distensibility of the arterial system. The ability of the arterial system to expand under normal physiological conditions helps to contribute to reducing ventricular load, maintaining normal blood pressure along the vasculature, reducing the traumatic effects of altered pressure on the vascular wall, and maintaining blood pressure homeostasis via unaltered baroreceptor functioning (Giannattasio & Mancia, 2002).

2.6.2 Measuring arterial stiffness

There are numerous methods of assessing arterial stiffness. The focus of this section will be on three commonly used measures of pulse pressure (PP), pulse wave velocity (PWV), and direct measurement. Each of these methodologies has its advantages and limitations which will be discussed briefly.

2.6.2.1 Pulse pressure

Pulse pressure refers to the difference between the systolic and diastolic pressure and is representative of the pulsatile nature of blood flow (Dart & Kingwell, 2001). Large population based studies have used pulse pressure of the brachial artery to identify the risk of cardiovascular disease (O'Rourke & Frohlich, 1999). For example, a recent report from the Framingham Heart Study has demonstrated that higher pulse pressure is important component of cardiovascular risk (Franklin, Khan, Wong, Larson, & Levy, 1999). The advantage of using the measure of PP as an indicator of arterial stiffness is the relative ease of measurement. Furthermore, local pulse pressure measurements can be made with instruments which utilize applanation tonometry. Thus, this simple measure of arterial stiffness is easily utilized in large population studies. The limitations of this technique include the ability of brachial artery blood pressure measurements to accurately reflect more central arterial pressures and the fact that alterations in blood pressure may not solely represent changes in arterial stiffness (Izzo, Jr., 2004).

2.6.2.2 Pulse wave velocity

Pulse wave velocity refers to the pulse transit time between a proximal artery (often carotid or aorta) and a distal artery (femoral). Typically the upstroke of the wave at two points is used to determine the time component of the equation. The distance

component is based on anthropometric measurements. When there is an increase in stiffness of the arterial tree, the wave travels faster as the artery's ability to expand is reduced (O'Rourke, Staessen, Vlachopoulos, Duprez, & Plante, 2002; Oliver & Webb, 2003; Izzo, Jr., 2004). PWV is influenced by both vascular geometry and the viscoelastic properties of the arterial wall and is defined by the Moens-Korteweg equation $PWV = \sqrt{(Eh \div 2\rho R)}$ where: E is Young's modulus of the arterial wall, h is wall thickness, R is arterial radius and ρ is the density of blood (Safar, London, Asmar, & Frohlich, 1998; O'Rourke et al., 2002). This method is quite accurate provided the measurement is made over an adequate amount of distance between recording sites to obtain accurate measurements (Izzo, Jr., 2004). With the advent of computerized algorithm to analyze PWV this has proven to be an accurate reproducible measure of arterial stiffness (Safar et al., 1998). Practical problems arise when points are assumed to be in line (i.e carotid – femoral line), when the characteristics of the arteries may change over time or with intervention, and in determining the distance between the two points using surface measurements (O'Rourke et al., 2002).

2.6.2.3 Direct measurement of arterial stiffness

The direct measurement of arterial stiffness is done by relating a change in vessel diameter (or area) to a change in pressure. This is accomplished through the use of simultaneous measurements of arterial diameter using ultrasound and changes in blood pressure. One major limitation of this approach is the blood pressure used as the distending pressure is obtained from the brachial artery and is used as the surrogate pressure for the carotid artery. This limitation can be partially overcome through the use of blood pressure tonometer placed over the artery of interest. The final limitation is

when a local measure of arterial stiffness is used as a global measure of arterial stiffness (O'Rourke et al., 2002; Oliver et al., 2003; Izzo, Jr., 2004).

2.6.3 Vascular stiffness in health and disease

Alterations in vascular stiffness are the result of a complex interaction which inevitably alters the functional and structural components of the vasculature. Increased stiffness can result from a reduction in endothelial function and an increase in endothelial layer permeability. At the intimal layer, an increase in collagen, a reduction in elastin and an increase in pro-inflammatory molecules can increase stiffness. In the media layer an increase in vascular smooth muscle and collagen, and a reduction in elastin can increase stiffness. In the adventitia increases in the amount of collagen can increase stiffness. The determinants of the alterations in vascular stiffening also include genetic predetermination, alterations in cellular signaling, and neuroendocrine signaling (Zieman et al., 2005).

When there is stiffening of the vasculature there is a subsequent alteration in the ventricular-vascular coupling. For a given stroke volume the left ventricle must work harder to eject the blood in a stiff aorta compared to a compliant aorta. This leads to left ventricular hypertrophy as the ventricle must pump the blood at a higher systolic pressure in order to maintain stroke volume (O'Rourke, 1990; Kass, 2002). The alterations in vascular stiffness induced by age and hypertension both lead to these deleterious effects on the heart and could at least partially account for increases in heart weight seen with normal aging and hypertension (Ferrari, Radaelli, & Centola, 2003). In addition to the alterations in left ventricular function, alterations in the ventricular vascular coupling alter coronary perfusion. When there is an increase in vascular stiffness, there is an

alteration in the timing of coronary perfusion such that there is an increase in coronary flow during systole instead of the normal perfusion during diastole. This alteration can impair coronary perfusion both at rest and during exercise (Dart et al., 2001; Kass, 2002).

Alterations in arterial stiffness also have a direct impact on blood pressure. Compared to younger subjects, older subjects display a widened pulse pressure. For example Kelly and colleagues, using applanation tonometry, demonstrated that the carotid artery pulse pressure increases by approximately 91% from the first to the last decade of life (Kelly, Hayward, Avolio, & O'Rourke, 1989). Similar studies have shown that the alterations in arterial stiffness in hypertensive and normotensive individuals are different following 6 years of follow-up. The results of this study demonstrated that both groups had increases in PWV over the 6-year period; however, the increase in PWV was more marked in the hypertensives compared to normotensive individuals (Benetos et al., 2002). These studies demonstrate that aging and hypertension both increase arterial stiffness, but those with hypertension have more marked increases in arterial stiffness.

This interrelation between age and arterial stiffness can be explained by examining the pressure and flow between young and old. When the stroke volume is ejected into a compliant aorta it expands and contracts to maintain a narrow pressure profile. When the stroke volume is ejected into a stiff aorta the pressure profile is widened. In a stiffer aorta a pressure wave is reflected sooner and arrives back during late systole opposed to arriving during early diastole (figure 1). This results in an increase in SBP and in an extreme case of stiffness can result in a reduction in DBP hence the widened pulse pressure (Smulyan & Safar, 1997; Izzo, Jr. et al., 2001; Dart et al., 2001;

Izzo, Jr., 2004). This clearly demonstrates the interrelationship between an elevated pulse pressure, hypertension and arterial stiffness.

Figure 1: Aortic pressure curves.
Note the earlier reflection in the wave on the right increasing systolic pressure and hence widening pulse pressure (Adapted from Izzo Jr, 2004).

Other standard cardiovascular risk factors also contribute to the development of arterial stiffness. Using PWV, Lehmann and colleagues examined the extent of arterial stiffness associated with a number of cardiovascular risk factors. They found a modest but statistically significant relationship ($R = -0.38$, $p<0.0001$) between aortic compliance and the number of cardiovascular risk factors (Lehmann et al., 1998). Similarly, Weber and colleagues examined the odds ratio of the presence of CAD assessed by angiography to augmentation index (another index of arterial stiffness). After controlling for height hypertension, high density lipoprotein, use of antihypetensives and statins, the odds ratio of developing coronary artery disease remained statistically significant ($OR = 2.00$ $p<0.05$) (Weber et al., 2004).

In summary, arterial stiffness increases with age as well as with hypertension and in the presence of a wide variety of cardiovascular risk factors. Furthermore, the interaction between arterial stiffness and hypertension is clearly bidirectional such that hypertension increases PP which in turn increases arterial stiffness. The effects of antihypertensive treatment on arterial stiffness in hypertension have been studied. The

results of these studies demonstrated that intensive treatment targeting a lower blood pressure significantly improves PWV and hence alters arterial stiffness whereas decreases to a moderate blood pressure does not alter PWV (Ichihara et al., 2003). In a similar study comparing the effects of an ACE inhibitor, calcium channel blocker and a diuretic on arterial distensibility, Honda and colleagues (1999) demonstrated that ACE inhibitors and calcium channel blockers significantly improved aortic distensibility, whereas diuretics did not improve aortic stiffness (Honda et al., 1999). As previously discussed exercise has the ability to alter resting arterial blood pressure, the next section will examine whether or not exercise can alter arterial stiffness.

2.6.4 Effects of exercise on arterial stiffness

2.6.4.1 Aerobic exercise

Early epidemiological and cross sectional studies first demonstrated that aerobic training could augment arterial stiffness. In a highly selected group of healthy older individuals Vaitkevicius and colleagues (1993) demonstrated that, even in the absence of cardiovascular disease (in both men and women) age was associated with a reduction in arterial stiffness. Endurance trained men, however, did not have as severe a reduction as their sedentary counter parts (Vaitkevicius et al., 1993). Subsequent studies have attempted to replicate these results. Contrary to these findings, results from the Atherosclerosis Risk In Communities study did not find a relationship between β-stiffness index and any form of physical activity (Schmitz et al., 2001). Tanaka, DeSouza and Seals (1998) confirmed the results of Vaitkevicius and colleagues. Tanaka *et al.* compared the effects of aging (indicated by menopausal status) in a group of physically active and sedentary women. They concluded that age was associated with an increase in arterial stiffness even in the absence of alterations in blood pressure, and the age related decreases in arterial stiffness were not observed in older highly physically active women (Tanaka, DeSouza, & Seals, 1998). Similarly, Monahan and colleagues (2001) examined the association between physical activity level and the alteration in baroreflex sensitivity and altered arterial compliance. Similar to Tanaka *et al.*, Monahan *et al.* recruited both active and sedentary individuals of both older and younger cohorts. The results indicated that age and habitual physical activity alterations in baroreflex function were significantly related to carotid artery stiffness (measured as carotid artery compliance). Baroreflex was measured as slope of the relation of the R-R interval and SBP in response to

phenylephrine. The results indicated that age and habitual exercise associated differences in both young and old subjects are related to the carotid arterial stiffness, as once changes in arterial diameter were controlled for, the effects of age and training were abolished (Monahan et al., 2001). Lastly, Kasikcioglu and colleagues (2005) compared aortic distensibility between young endurance trained athletes to a group of sedentary controls. The results of this study further demonstrated that habitual activity was associated with a reduction in arterial stiffness (2.77±0.28 and 3.43±0.41 arbitrary units, $p<0.001$) (Kasikcioglu, Kayserilioglu, Oflaz, & Akhan, 2005).

The previous cross sectional and single prospective study are suggestive that habitual forms of endurance type activity are beneficial at reducing age associated declines in arterial stiffness. However, data can not be inferred about the potential mechanisms or as to the exact causes of the improved arterial stiffness. Prospective studies are required in order to determine the potential mechanisms of exercise induced improvements in arterial stiffness.

The first prospective study to examine the effects of aerobic training on systemic arterial compliance was conducted by Cameron and Dart (1994). In this pseudo cross-over design two groups completed four weeks of cycle ergometry training at 75% of their maximum workload preformed 2×/week. Following four weeks of training, both groups exhibited significant improvements in systemic arterial compliance and a reduction in stiffness index (mean change = +0.25 ACU and -1.03, $p<0.05$ respectively). They suggested that alterations in endothelial function, circulating levels of vasoconstrictors, and sympathetic tone accounted for the improvements seen in systemic arterial compliance (Cameron et al., 1994). Similarly, Kakiyama and colleagues (2005) examined

the effects of short term endurance training on aortic distensibility in a group of healthy males. Briefly, they trained at 70% of the maximal oxygen consumption 3 – 4 days per week for 8 weeks. Measures of aortic distensibility were made using aortic pulse wave velocity (aortic – femoral). Following training, there was a significant reduction in APWV which remained significant 2 weeks into the detraining period before retuning to baseline values (Kakiyama et al., 2005). The results of these studies demonstrate that moderately intense exercise can improve arterial compliance in normal healthy young individuals.

Contradictory results were seen in a group of patients with isolated systolic hypertension. Following 8-weeks of thrice weekly training at 65% of maximum heart rate there were significant improvements in the maximum oxygen uptake in the training group compared to the control group. The training did not have any effect on systemic arterial compliance (0.36±0.06 to 0.38±0.06 $p>0.05$) or on aortic input impedance (2.7±0.29 to 2.75±0.39, $p>0.05$). The authors suggested that arterial stiffness in these patients was resilient to change (Ferrier et al., 2001). Parnell and colleagues (2002) examined the effect of exercise training on systemic arterial compliance and PWV in a group of patients with heart failure (stages II – III). The exercise protocol was based on an initial level of 50-60% of the maximum heart rate 30 minutes per day 5-7 days per week which progressed to 60 minutes of exercise following 8 weeks. As expected exercise significantly improved exercise capacity as assessed by a 6-minute walk test, and resulted in a reduced heart rate. As hypothesized, systemic arterial compliance (assessed using augmentation index) was improved following 8-weeks of training; however, no effects of training were observed in central (carotid-femoral) or peripheral (femoral-dorsalis pedis)

PWV (Parnell, Holst, & Kaye, 2002). Lastly, Edwards and colleagues examined the effects of standard cardiac rehabilitation on arterial stiffness in a group of patients with CAD. Following 12 weeks of training arterial stiffness was reduced, as indicated by a 30% reduction in the augmentation index in the exercise trained group (Edwards et al., 2004).

The results of this latest group of studies is suggestive that aerobic training can improve reduced arterial stiffness associated with heart failure and CAD however, exercise may not be beneficial at improving arterial stiffness in individuals with isolated systolic hypertension. One possible discrepancy between these studies was the training protocol utilized. Ferrier *et al.*, used a relatively low intense exercise protocol with no progression where as both Parenell and colleagues and Edwards and colleagues used higher intensities and progression over the duration. Furthermore, the training intensities utilized in the participants without cardiovascular diseases also used more intense programs. This suggests that training intensity may be important for adaptations in arterial stiffness to occur.

The mechanisms that have associated with the alteration in large artery stiffness were recently reviewed. Seals (2003) suggested that exercise may alter the elastin/collagen ratio and hence reduce some of the age associated increases in collagen. Furthermore, alterations in non-structural component such as endothelial function may reduce the increase in vascular smooth muscle tone associated with age and disease. Lastly exercise may reduce cardiovascular risk factors if the duration of training is of sufficient length (Seals, 2003).

2.6.5.2 Resistance exercise

Unlike aerobic training, the effectiveness of resistance training as a tool to improve arterial stiffness is not as well understood. This is one area in which more research is required before a definitive conclusion can be reached. Early cross sectional studies were the first to examine the effects of resistance training on arterial stiffness. Bertovic and colleagues (1999) examined the effects of resistance training in a group of resistance trained males compared to non-exercising controls. Those who resistance trained had a significantly lower systemic arterial compliance compared to the non-exercisers (0.40±0.04 vs. 0.54±0.04 arbitrary units, $p<0.01$). Furthermore, the stiffness of the proximal aorta was also significantly stiffer in the resistance trained individuals compared to the controls (4.6±0.2 vs 3.8±0.4). The authors concluded that the difference in compliance was not related to differences in systemic pressure, but a result of alterations in intrinsic vessel properties (Bertovic et al., 1999). Miyachi and colleagues (2003) attempted to determine if the effects of aging and resistance training were additive at reducing central arterial stiffness. They compared sedentary and resistance trained young and middle-aged individuals. The resistance trained middle-aged men exhibited carotid artery compliance 30% lower than there age matched sedentary men. In addition, the resistance trained middle-aged men had stiffer arteries than the young resistance trained men. This indicates that resistance training had an additive effect with aging at increasing arterial stiffness (Miyachi et al., 2003). Unlike the results of Bertovic *et al.*, Miyachi *et al.* failed to show a significant reduction in carotid artery compliance in resistance trained young men compared to the sedentary young men.

The results of these studies are quite compelling and suggest that resistance training may have a negative influence on the vasculature by increasing the stiffness of

the central arteries. More recent studies have examined the direct influence of resistance training using prospective studies. Miyachi *et al.* (2004) used a thrice weekly resistance training program of 80% MVC, 12 repetitions/set and a total of 3 sets per training session training progressed provided that 10 repetitions were completed in the third set. The training used a combination of upper and lower body exercises. Following 8 weeks of training, there were significant reductions in arterial compliance, and significant increases in stiffness index ($p<0.01$ for both). The stiffness was maintained for the duration of the training, but returned to near baseline values following 8 weeks of detraining. No significant changes were observed in indices of left ventricular hypertrophy or peripheral arterial compliance. Rakobowchuk and colleagues (2005) utilized a more intense resistance training program. Subjects trained 5 days per week using a 3 day split routine. The focus of the resistance training program was to develop hypertrophy so the participants were constantly motivated to lift as much as they could. Following 12 weeks of training, there was a significant reduction in pulse pressure because of a small but significant increase in DBP. Contrary to all previous studies, Rakobowchuk and co-workers found no deleterious effects of resistance training on either compliance or stiffness index. Similar to previous reports there were no changes in left ventricular structure or left ventricular mass (Rakobowchuk et al., 2005).

These two prospective studies clearly demonstrate that more research into the effects of resistance training and arterial stiffness need to be preformed. Future studies should focus on the potential mechanisms of altered arterial stiffness. Longer prospective studies involving both young individuals and older individuals are required to fully examine this issue.

3.0 Materials and Methods

3.1 Subjects

A total 20 participants (16 male, 4 female) all medicated to treat hypertension were recruited from the Centre for Health Promotion and Rehabilitation (Mac Seniors and Mac Turtles exercise programs). All participants were asked to maintain their current physical activity, nutritional habits and medications throughout the study. Two of the 20 participants were excluded because of medication changes, and 1 participant voluntarily withdrew. The current investigation and procedure detailed within were approved by the Hamilton Health Sciences Research Ethics Board.

The inclusion criteria were any individual being pharmacologically treated with anti-hypertensive medication. Individuals were excluded and were ineligible to participate in the study if they had diabetes, heart failure, current smoker, or if they were being treated with hormone replacement therapy. All testing procedures occurred in Vascular Dynamics Laboratory at McMaster University, and training sessions took place in the Centre for Health Promotion and Rehabilitation and at the participants' homes.

Subjects who chose to participate were called and scheduled for an individualized information session and subsequent familiarization. The information session consisted of a detailed description of the study and the opportunity to review and sign informed consent. If the individual signed the informed consent, they underwent a familiarization session which consisted of ten minutes of supine rest, followed by three consecutive measures of arterial blood pressure (see following description).

3.2 Study Design

This study consisted of 8-weeks of unilateral isometric handgrip training with pre and post assessment of cardiovascular responsiveness. The participants trained twice weekly prior to beginning their normal exercise routine in the Centre for Health Promotion and Rehabilitation. The third training session was completed at home. All testing procedures occurred prior to and following the 8-weeks of training. This study employed a single group repeated measures design.

3.3 Training Protocol

The training protocol consisted of 8 weeks of unilateral isometric handgrip training of the non-dominant hand using a commercially available handgrip device (Cardiogrip Corp, Westerville, Ohio). Each training session consisted of a 5 minute rest followed by a blood pressure measurement via automated oscillometry (Dynamap Pro 100 V2, GE Medical Systems, Tampa FLA, USA). After blood pressure measurement, the participants participated in a 5 minute warm-up on a cycle ergometer or on a treadmill, at a low to moderate intensity. The handgrip training consisted of 4, 2-minute isometric contractions at 30 % of the individual's repetition max (1-RM). Each contraction was separated by a four minute relaxation period. During each exercise session participants were required to perform a 1-RM, followed by approximately 30 seconds of rest, prior to handgrip training. This protocol was repeated twice weekly in the Centre for Health Promotion and Rehabilitation and once weekly at the participant's home. For each training session, the participants sat, placed their non-dominant forearm on top of the table, and were instructed to keep their elbow and forearm on the table while performing the IHG. Trainers monitored the participants during their sessions in

the Centre for Health Promotion and Rehabilitation to ensure proper positioning and to keep the participant motivated during the training.

3.4 Testing Protocol

All testing sessions occurred in the Vascular Dynamics Laboratory at McMaster University. As previously indicated all participants visited the laboratory and were familiar with the techniques utilized during the investigation. Participants were requested to abstain from vigorous physical activity for twenty-four hours, caffeine for twelve hours, and all food for at least four hours prior to all testing session. Prior to the final testing session the participants were requested to repeat the meal they had consumed prior to the initial testing session. All testing sessions were performed in a temperature controlled room (22 – 24°C).

3.4.1 Heart Rate

Heart Rate (HR) was monitored via two separate electrocardiogram (ECG) systems in the standard 3 lead placement (CM 5). The ECG signal was captured using bio-amplifier an analogue to digital signal converter (Powerlab 16sp, ADInstruments, Colorado Springs, CO, USA) sampled at 200 Hz, collected by Chart 5 (ADInstruments, Colorado Springs, CO, USA) and subsequently stored on a computer (IBM Nevista x86 compatible processor, White Plains, NY, USA) for later off-line analysis. The second ECG signal was processed internal to the Ultrasound system (System FiVe, GE Medical Systems, Horten, The Netherlands).

3.4.2 Blood Pressure

Supine blood pressure was assessed at the familiarization session and at the onset of both testing sessions. Participants were equipped with a standard arterial blood pressure cuff placed around the upper arm. Blood pressure was assessed following ten minutes of supine rest in a dark, quiet, temperature controlled room using an automated oscillometric device (CBM-7000, Colin Medical Instruments, San Antonio, TX, USA) in triplicate at minutes twelve, fourteen and sixteen. The three systolic and three diastolic blood pressures were averaged to obtain single measures of resting systolic and diastolic blood pressure.

During the remainder of the testing procedure, continuous blood pressure was obtained using radial artery tonometry calibrated to brachial artery blood pressure (CBM-7000, Colin Medical Instruments, San Antonio, TX, USA). The tonomoter was placed over the radial artery at the point of maximal pulsation and secured. This allowed for acquisition of continuous pressure waveforms from the radial artery. Blood pressure signals were processed by an analogue to digital signal converter (Powerlab 16sp, ADInstruments, Colorado Springs, CO, USA) sampled at 200 Hz, collected by Chart 5 (ADInstruments, Colorado Springs, CO, USA) and subsequently stored on a computer (IBM Nevista x86 compatible processor, White Plains, NY, USA) for later off-line analysis.

3.4.3 Rate Pressure Product

Rate Pressure Product (RPP) which is an indicator of myocardial oxygen demand was calculated as the product of heart rate and systolic blood pressure (White, 1999).

$$RPP = HR \times SBP \qquad \text{(Equation 1)}$$

This was calculated beat-by-beat during the entire isometric handgrip testing protocol.

3.4.4 Cardiac Output

Stroke velocity was measured non-invasively using a 2.0 MHz continuous wave Doppler ultrasound probe (GE Vingmed CFM 800, Horten, Norway). The probe was placed in the suprasternal notch and angled toward the ascending aorta. The aortic flow was identified by its large positive peak. Only the maximal velocity was sampled to accurately represent peak aortic flow during systolic ejection. The maximal velocity signal was converted to a digital signal (Powerlab 16sp, ADInstruments, Colorado Springs, CO, USA) sampled at 200 Hz, collected by Chart 5 (ADInstruments, Colorado Springs, CO, USA) and subsequently stored on a computer (IBM Nevista x86 compatible processor, White Plains, NY, USA) for later off-line analysis. Stroke velocity was determined by multiplying the maximum velocity obtained by the ejection time which was subsequently multiplied by the duration of the cardiac cycle.

$$\text{Stroke velocity} = \text{Maximum velocity} \times \text{Ejection time} \times \text{heart rate} \qquad \text{(Equation 2)}$$

Aortic root diameters were assessed using Brightness mode (B-mode) parasternal long-axis ultrasound images obtained in the supine position with a 2.5 MHz ultrasound probe (GE Vingmed System FiVe, Horten, Norway). Depth, gain, brightness and contrast

were adjusted to acquire a clear image of the aortic valves and the aorta. Images during three consecutive heart cycles were collected and stored digitally and on S-VHS video tape. Additional images were also obtained from participants in the left lateral decubitus position. Measures of aortic diameter were made at the insertion point of the aortic valves at end-systole and end diastole (Miyachi, Iemitsu, Okutsu, & Onodera, 1998; Rowland, Melanson, Popowski, & Ferrone, 1998; Nottin et al., 2002; Sugawara et al., 2003). Digital 2-D images were measured using a commercially available software package (EchoPAC V.6.2, GE Vingmed Ultrasound, Horten, Norway). This software allows the conversion of the 2-D image to anatomical M-mode tracing. Briefly, an anatomical M-mode line was inserted perpendicular to the insertion points of the aortic valves. This line was then converted to an M-mode tracing for the entire image. Digital calipers were used measure the aortic ring diameter using the leading edge to leading edge technique. Aortic root diameter (ARD) was calculated as in equation 3. Resting ARD was used to calculate cardiac output throughout the exercise session.

$$\text{ARD} = 2/3 \text{ Diastolic Diameter} + 1/3 \text{ Systolic Diameter} \qquad \text{(Equation 3)}$$

Cardiac output ($\dot{Q}$) was calculated by multiplying stroke velocity (SV) by ARD

$$\dot{Q} = ((\text{ARD} \div 2)^2 \times \pi) \times \text{SV} \qquad \text{(Equation 4)}$$

Cardiac output was assessed during supine rest, seated rest and the transition periods between rest and exercise. The $\dot{Q}$ during 10 continuous heart cycles was averaged to represent cardiac output during the transition periods between rest and exercise.

3.4.5 Aortic Stiffness

Aortic pulse pressure was inferred from carotid artery pulse pressure obtained via external applanation tonometery. Previous studies have determined that the non-invasive external pressure tracings of the carotid artery are not significantly different than intra-aortic pressures (Cameron et al., 1994; Chen et al., 1996). The carotid artery was palpated by hand then a pen-like tonometer (SPT-301, Millar Instruments Inc. Texas, USA) was placed over the carotid artery at the point of the strongest pulsation. Carotid artery pulse pressure was measured, simultaneous with measurement of radial artery pulse pressure via applanation tonometry (as described previously). The pressure obtained from the hand-held tonometer is subject to hold down pressure and is an un-calibrated signal. Therefore, the carotid pulse pressure tracing was calibrated to the pressures obtained at the radial artery. The DBP and mean blood pressures at the radial artery were set as the DBP and mean blood pressure in carotid artery (Miyachi et al., 2004; Rakobowchuk et al., 2005). This is based on the assumptions that mean arterial pressure does not change in large conduit arteries, and diastolic blood pressure is not significantly different in the carotid, brachial and femoral arteries (Kelly et al., 1989). However, SBP does change in different portions of the arterial tree as a result of pulse pressure amplification as the pulse travels to smaller arteries; therefore, the SBP obtained in the radial artery would overestimate the pulse from the carotid artery (Izzo, Jr. et al., 2001). Systolic blood pressure was therefore determined using an extrapolation technique (Miyachi et al., 2004; Rakobowchuk et al., 2005).

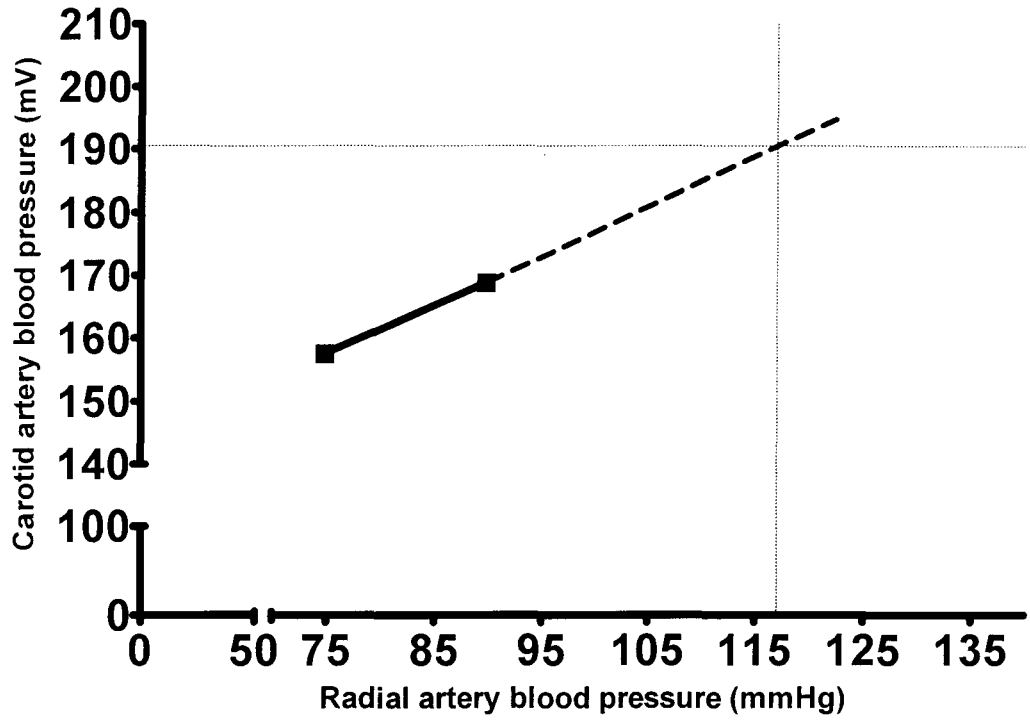

Figure 2. Calibration of tonometer
Use of extrapolation technique to determine carotid artery systolic blood pressure, by assigning radial artery diastolic blood pressure and mean arterial pressure as the diastolic blood pressure and mean arterial pressure obtained from the carotid artery and extrapolating this relationship.

Aortic diameter was assessed using B-mode ultrasound images obtained by using a 2.5 MHz ultrasound probe (GE Vingmed System 5, Horten Norway). This method has been previously described (see aortic root diameter). Aortic stiffness measurements were measured 3 cm above the insertion point of the aortic valves. Using the digital 2D image a straight line was drawn between the insertion points of the aortic valves using electronic callipers. From this line a second measurement was made 3 cm distal from the original site, and the end of the line was landmarked. Using the landmarked point, an anatomical M-mode line was inserted perpendicular to the arterial walls.

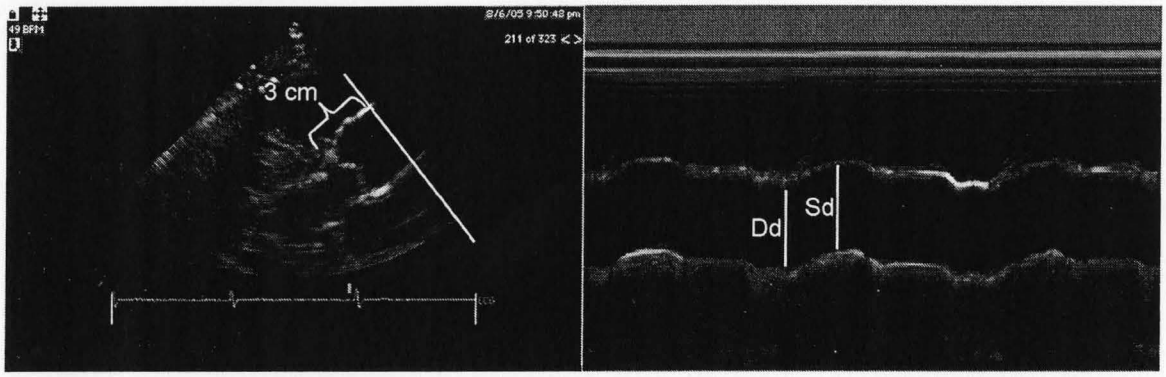

Figure 3. B-mode (left) and Anatomical M-mode (right).
Sd, systolic diameter; Dd, diastolic diameter.

All measurements were made using M-mode tracing and utilizing the leading edge to leading edge technique. The systolic diameter (Sd) was defined as the diameter at maximal anterior motion of the aorta (occurring just after the peak of the T-wave on the ECG) and the diastolic diameter (Dd) was defined as the diameter that occurred at the peak of the QRS complex (Stefanadis, Stratos, Boudoulas, Kourouklis, & Toutouzas, 1990; Stratos, Stefanadis, Kallikazaros, Boudoulas, & Toutouzas, 1992; Eren et al., 2004). Reproducibility of this technique was assessed using the coefficient of variation and the method error. For the systolic area, the reproducibility was 0.08 % and 0.10 %. The coefficients of variation were 2.85% and 2.86% for systolic and diastolic area respectively. The coefficient of variation for area change was 16.19%, and the Method Error was 0.38%.

Distensibility was calculated using the change in aortic area (ΔA) and the carotid artery pulse pressure (PP). Change in arterial area was assessed using the arterial diameters during systole and diastole from the cardiac images and diameter analysis previously described (Stefanadis et al., 1990; Stratos et al., 1992; Eren et al., 2004).

$$\Delta A = \pi \times (Sd/2)^2 - \pi \times (Dd/2)^2 \qquad \text{(Equation 5)}$$

Pulse pressure was determined by the difference between the systolic and diastolic pressures in the carotid artery. Ten consecutive pressure wave forms were used to determine systolic (peak) and the diastolic (trough) pressures.

$$PP = SBP - DBP \qquad \text{(Equation 6)}$$

Distensibility (AD) was assessed as the relative change in aortic area for a given change in pressure (O'Rourke et al., 2002).

$$AD = \Delta A \div (PP \times (\pi \times (Dd/2)^2) \qquad \text{(Equation 7)}$$

The distensibility was calculated for each image then averaged to determine the final value for aortic distensibility.

The other index of arterial stiffness utilized in this investigation was β-stiffness index (SI). This is the logarithm of the ratio of systolic to diastolic pressure to the relative change in area (O'Rourke et al., 2002).

$$SI = Ln\ (SBP/DBP) \div (\Delta A \div (\pi \times (Dd/2)^2) \quad \text{(Equation 8)}$$

Area change was averaged over both images, and the average of 10 consecutive measures of SBP and DBP were utilized in the above equation.

3.4.6 Continuous Isometric Handgrip Protocol

Following the measurement of aortic stiffness, the participants were assisted and moved from a supine position to a seated position in a chair at a training table. One minute of continuous resting HR, BP, and stroke velocity was collected. Following this the participant began the training. All parameters (HR, BP, SV) were measured continuously during the IHG protocol starting at the onset of the first contraction, and continued until the end of the last rest period four minutes after the end of the last contraction using the methods previously described. In order to assess whether there were training induced changes in the cardiovascular response to a workload of the same

absolute intensity both pre and post training. The pre training MVC was recorded. The automated IHG protocol is initiated by a maximal voluntary contraction and the exercising workload is automatically determined from the initial input. Therefore, during the post-training assessment an investigator, rather than the participant, performed the initial MVC on behalf of the participant, in order to ensure that the correct workload was achieved. This procedure allowed for the comparison of the cardiovascular response at the same absolute intensity.

All data was subsequently analyzed using a beat-by-beat method, by gaiting the R-R intervals of the heart rate. The subsequent data was averaged to provide data from 0 seconds (onset of contraction 1) to 1440 seconds (end of rest period four).

3.5 Statistical Analysis

All data are presented as mean ± standard error of the mean (SEM). Differences pre and post were analyzed using a 1-way repeated measures analysis of variance (ANOVA) for resting blood pressure and measures of arterial stiffness. For the continuous data (HR, BP, RPP) the data during the final 10 seconds of each contraction were averaged to obtain a single measure for the end of the contraction. For cardiac output, data for the transition periods exercise into rest were analyzed to see if there was hyperemic flow. These data were analyzed using a 2-way Repeated measures ANOVA (Phase × Time). Post hoc analyses were performed using Tukey's HSD analysis. All statistical analysis was conducted using a commercially available software package (Statistica 6.0, Stat Soft Inc., Tulsa OK, USA). A p-level ≤ 0.05 was considered to be statistically significant.

4.0 Results

4.1 Participant Characteristics

Complete participant characteristics can be seen in Table 1. As it would be anticipated, the medications of participants varied greatly and six were on multiple drug regimens.

Table 1. Participant characteristics

Characteristic	
Age	66.41 ± 1.48
Height (cm)	178.46 ± 3.10
Weight (kg)	85.78 ± 4.31
Time on Meds (years)	8.54 ± 1.85
CAD (#)	7
Medications	
ACE-I	6
β-B	1
CCB	1
Diuretic	3
ACE-I + βB	3
ACE-I + CCB	1
ACE-I + Diuretic	1
ACE-I + βB + CCB	1

Data are presented as mean ± SEM. CAD, coronary artery disease (as assessed by medical questionnaire). ACE-I, angiotensin converting enzyme inhibitor; β-B, beta blocker; CCB, calcium channel blocker.

4.2 Effects of training on resting cardiovascular measurements

Following 8 weeks of training there were no significant improvements in resting systolic blood pressure (125.33 ± 2.53 to 121.39 ± 2.31) resting or diastolic blood pressure (71.92 ± 2.15 to 69.78 ± 2.13 mmHg, figure 3). Resting heart rate remained unchanged (56.10±2.26 to 54.78±1.82 beats/minute). Lastly, there was no change in resting cardiac output (4.43±0.34 to 4.81±0.45 L/minute, n=16).

4.3 Effects of training on indices of aortic stiffness

Following 8 weeks of unilateral IHG there were no improvement seen in carotid artery pulse pressure. Furthermore, there were no significant changes in aortic distensibility or stiffness index (Table 2). Data were available for fifteen participants as two participants had inadequate aortic images to allow for analysis.

Table 2. Effects of training on indices of aortic stiffness

	Pre	Post
CAPP (mmHg)	43.8 ± 2.6	42.8 ± 2.5
Distensibility ($mmHg^{-1}$)	0.00306 ± 0.00029	0.00352 ± 0.00048
Stiffness Index (non dimensional)	3.32 ± 0.09	3.27 ± 0.15
Systolic diameter (cm)	3.17 ± 0.11	3.17 ± 0.10
Diastolic diameter (cm)	2.99 ± 0.11	2.97 ± 0.10
Aortic root diameter (cm)	2.11 ± 0.04	2.09 ± 0.04

Data are presented as mean ± SEM. CAPP, carotid artery pulse pressure.

4.4 Acute cardiovascular response and adaptations

4.4.1 Arterial blood pressure

With each contraction both pre and post training increases in both systolic and diastolic blood pressure throughout the entire contraction and these values returned to near rest values shortly after the end of the contraction (Figure 3). When the SBP for the last 10 seconds of each contraction phase was averaged, there were no differences in the acute SBP responses as a main effect for phase was noted such that contraction 4 had a higher SBP than rest and contractions 1 and 2. During contractions 1 through 4 SBP increased by 8, 7, 10 and 20 mmHg respectively over rest. The resting diastolic blood pressure was less than the DBP for the last 10 seconds of each contraction phase (Figure 5). The average blood pressure during the final 10 seconds of contraction 4 was significantly greater then the DBP at the end of contractions 1 and 2. During contraction 1 – 4 DBP increased by 6, 6, 8, and 14 mmHg respectively compared to rest (Figure 5)

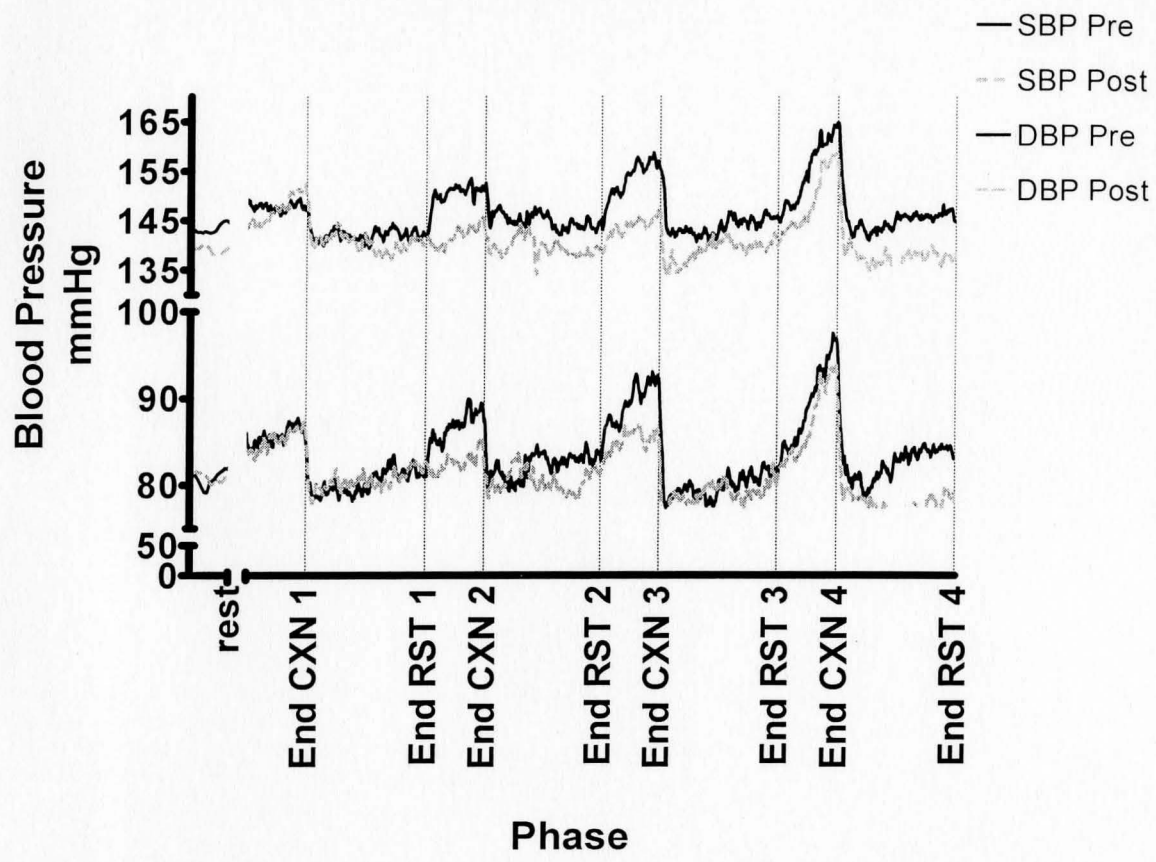

Figure 4. Acute blood pressure response to IHG.
Data are beat-to-beat data for n=13 participants. SBP, systolic blood pressure; DBP, diastolic blood pressure; CXN, contraction; RST, rest.

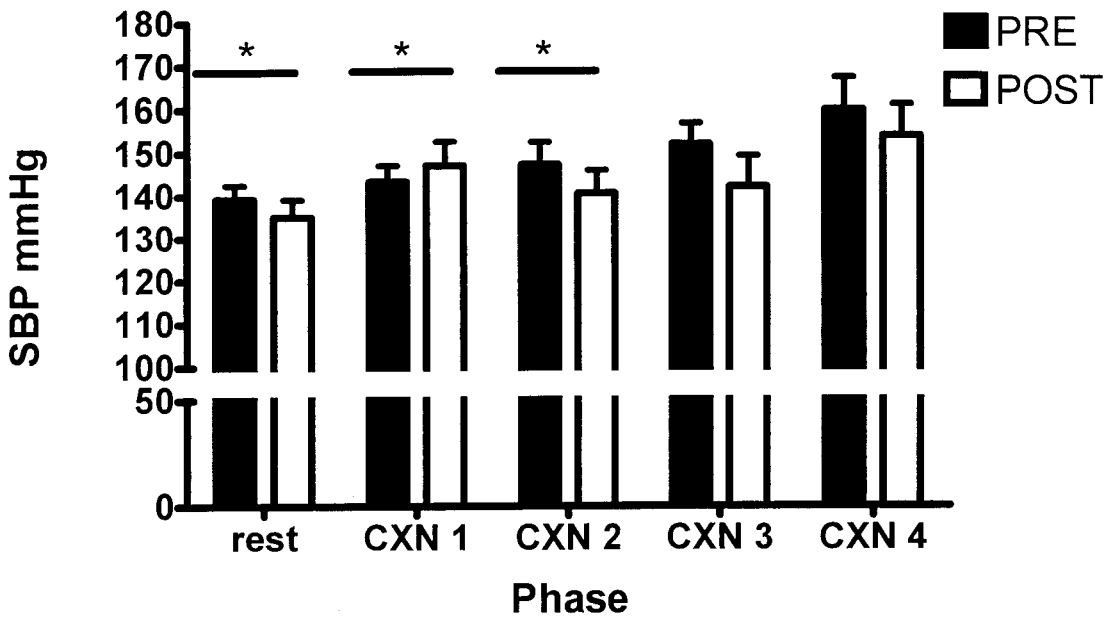

Figure 5. Average systolic blood pressure of the final 10 seconds of each contraction. Data are presented as mean ± SEM. CXN, contraction. * Significantly different from contraction 4 (main effect for time, $p<0.05$, $n=13$).

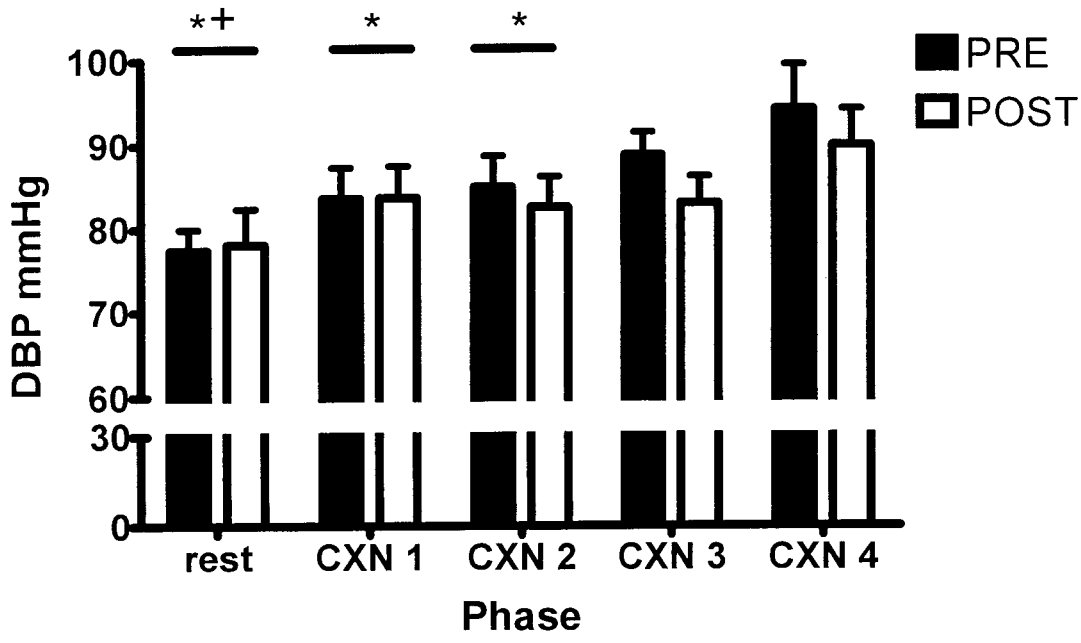

Figure 6. Average diastolic blood pressure of the final 10 seconds of each contraction. Data are presented as mean ± SEM. CXN, contraction. *, Significantly different from contraction 4 (main effect for time, $p<0.05$); +, significantly different from contractions 3 ($p<0.05$, $n=13$).

4.4.2 Heart rate

At the onset of each period of IHG contraction there was a rapid rise in heart rate which peaked at the end of the contraction, followed by a return towards baseline values during the rest periods (Figure 6). The acute HR response to IHG exercise was not altered with 8 weeks of IHG training. The heart rate during the final 10 second of each contraction phase was significantly higher than the heart rate at rest both pre and post (Figure 7). The average heart rate during the final 10 seconds of the contraction 4 was also significantly higher than the heart rate observed during contractions 1 – 3 (Figure 7).

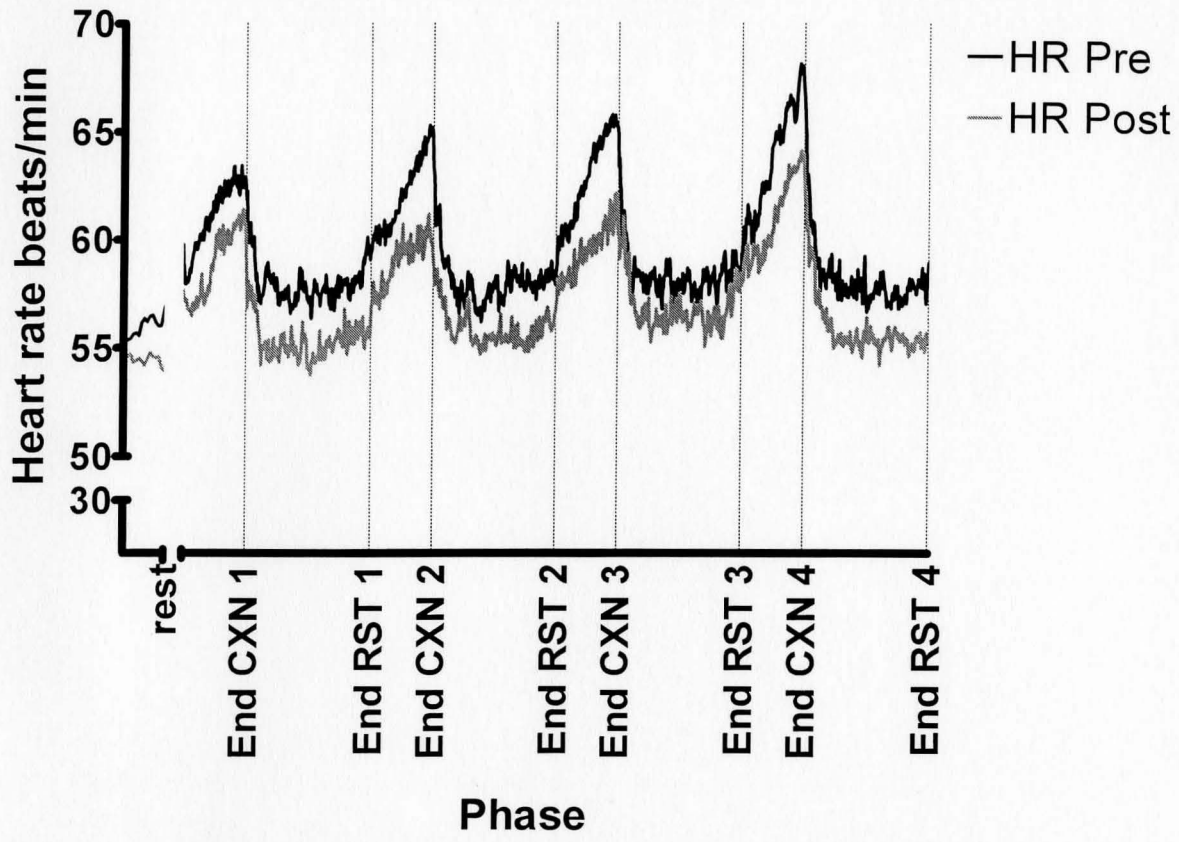

Figure 7. Acute heart rate response to IHG.
Data is average of 15 participants. CXN, contraction; RST, rest.

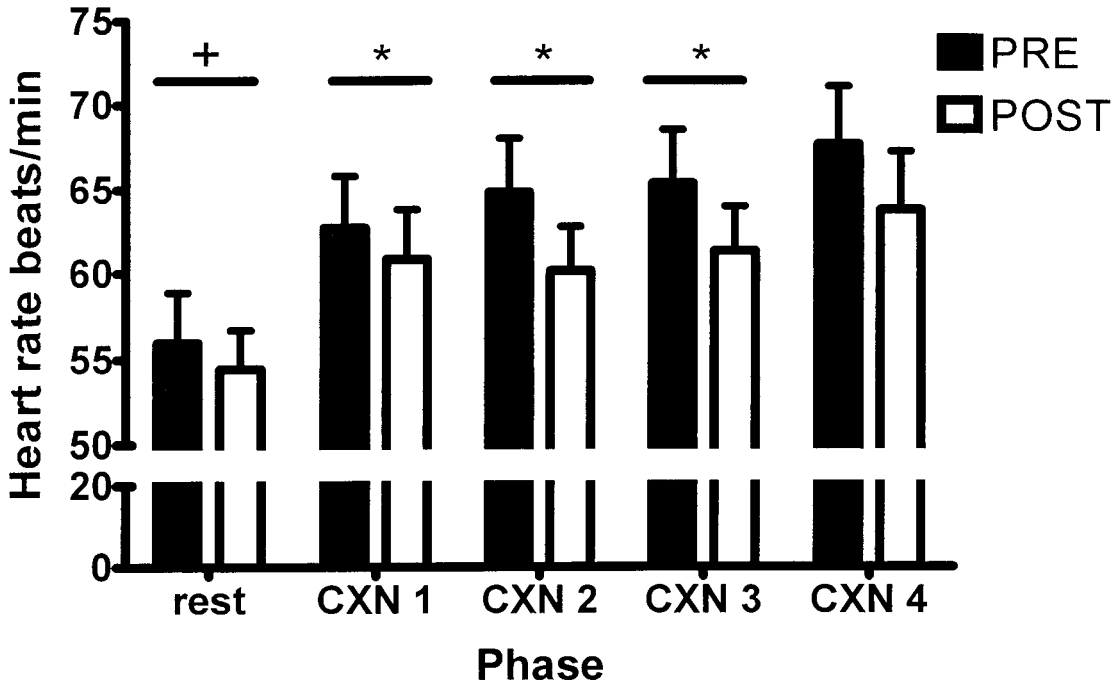

Figure 8. Average heart rate of the final 10 seconds of each contraction.
Data are mean ± SEM. CXN, contraction. *, significantly different from contraction four ($P<0.05$), +, significantly different from all contractions $p<0.05$ ($n=15$).

4.4.3 Rate pressure product

The RPP response to IHG showed a similar response to that observed for heart rate, such that there were marked increases during the contraction phase which returned toward baseline during the rest periods (Figure 8). Average increases from rest for contractions 1 – 4 were 1391.1, 1443.9, 1761.9 and 2789.7 beats×mmHg×min^{-1}. Myocardial oxygen demand, as indicated by RPP was elevated at the end of each contraction phase compared to rest and further elevated at the end of contraction 4 compared to all other contraction phases (Figure 9).

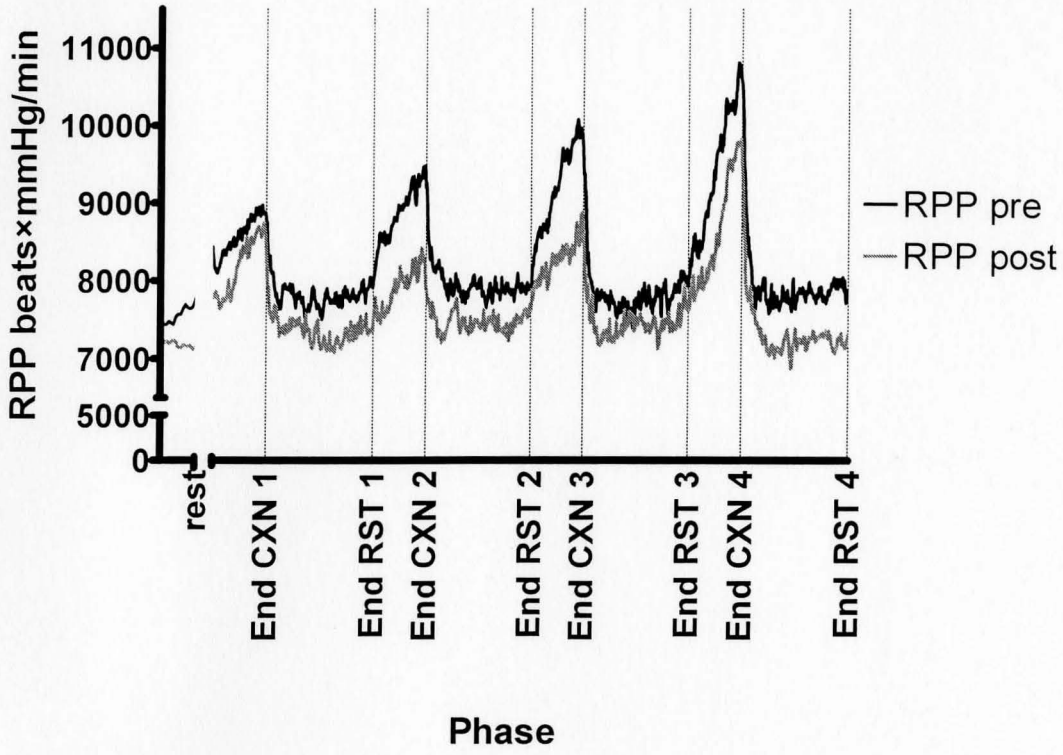

Figure 9. Acute rate pressure product response to IHG.
Data are beat-to-beat data for n=13 participants. CXN, contraction; RST, rest.

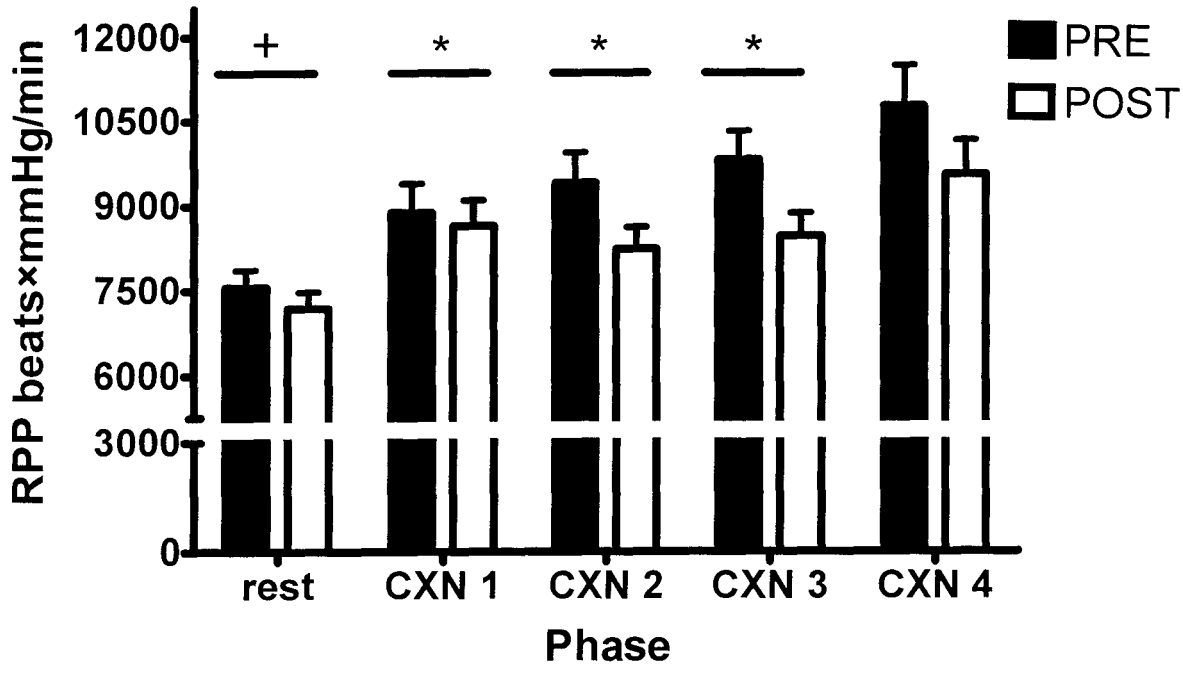

Figure 10. Average rate pressure produce of the final 10 seconds of each contraction. Data are mean ± SEM. CXN, contraction. *, significantly different from contraction four ($P<0.05$), +, significantly different from all contractions $p<0.05$ ($n=13$).

4.4.4 Cardiac output

A main effect for phase was observed such that supine rest was significantly different from the start rest 2, end of contraction 3 and start of rest four. The cardiac output response to IHG exercise was not altered by 8 weeks of handgrip training (Figure 10). During each contraction $\dot{Q}$ increased from the onset to the end of the contraction and the elevated $\dot{Q}$ was maintained and increased slightly at the onset of each rest period, but returned toward baseline levels at the end of each rest period (Figure 10).

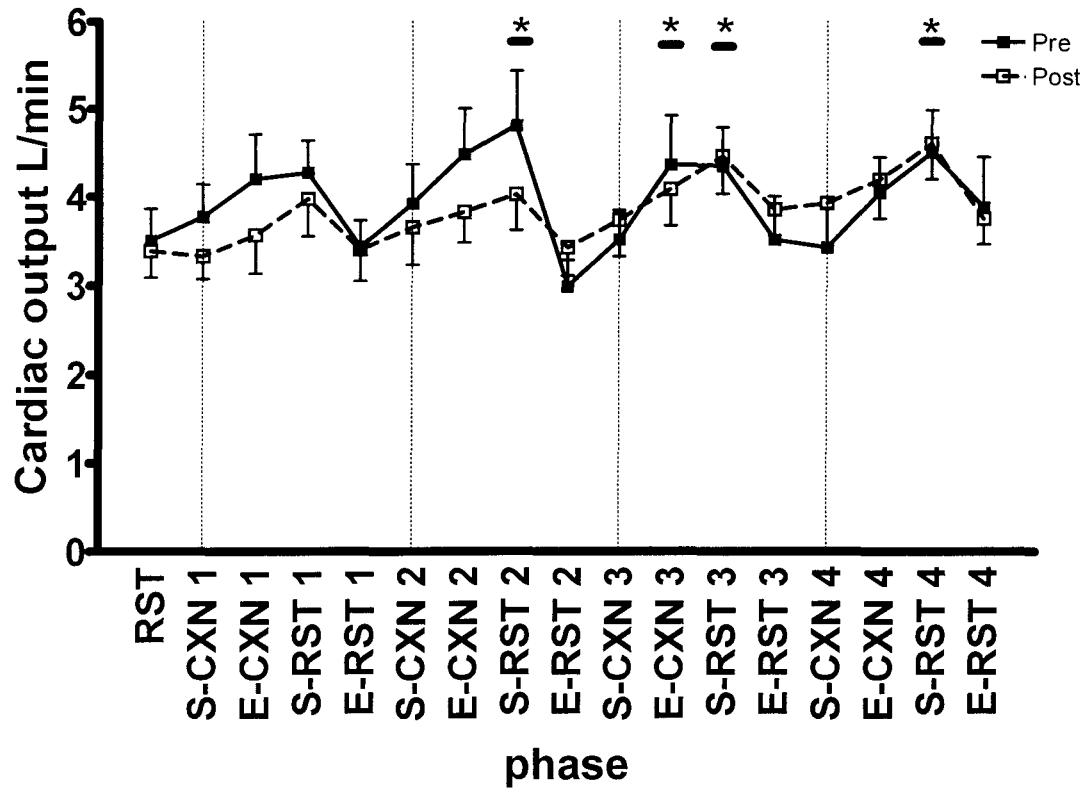

Figure 11. Cardiac output for transition periods
Data are 10 second average intervals for n=12 participants. E, end; S, Start; CXN, contraction; RST, rest. *, significantly different from rest.

5.0 Discussion

Contrary to the initial hypothesis, 8-weeks of unilateral handgrip training did not reduce resting arterial blood pressure; however, heart rate cardiac output did remain unaltered with training. Furthermore, there were no training induced differences observed in any measure of aortic stiffness or in the acute cardiovascular response to IHG exercise. Lastly, isometric handgrip exercise did result in acute increases in heart rate, blood pressure (both systolic and diastolic), rate pressure product and cardiac output.

5.1 Acute cardiovascular response

It is currently well established that in response to isometric exercise there is an increase in heart rate and blood pressure and subsequently RPP, as a result of a combined central and peripheral stimulation. Central command directly stimulates the cardiovascular control centre, while peripherally the direct stimulation of mechanosensitive and chemosensitive nerve endings (group III and IV afferents) further stimulates the cardiovascular centre in the medulla (Shepherd, Blomqvist, Lind, Mitchell, & Saltin, 1981).

To date, no study which utilized isometric handgrip training as a tool to reduce arterial blood pressure has fully documented the cardiovascular response to this form of exercise. The first study which attempted to identify the cardiovascular response was Wiley and co-workers (1992). In this study, blood pressure was measured using a mercury sphygmomanometer and stethoscope during the final 30 seconds of the first isometric contraction phase. Increases in both systolic (16.8 ± 1.01 mmHg) and diastolic pressure (15.9±0.90 mmHg) were observed (Wiley et al., 1992). Similarly Ray and Carrasco (2000) used the second minute of the first contraction to assess the increase in

MAP during the isometric handgrip contraction. Unlike Wiley and colleagues, Ray and Carrasco obtained continuous blood pressures using a Finapres device. In response to contraction they demonstrated ~18 mmHg increase in mean arterial pressure (Ray et al., 2000). The results of the current investigation are contrary to these findings. Specifically we demonstrated only a moderate increase in SBP and DBP during the first contraction (~ 4 and 5 mmHg increase respectively). One potential difference between the response observed in this study and previous studies can be explained by the differing populations. Wiley *et al.* recruited a group of elevated normotensive individuals with a mean age 27.5, and Ray and Carrasco also used a normotensive population mean age 27 years old whereas the current investigation was a population of medicated hypertensives with a mean age of 66 years old. Boutcher and Stocker (1999) compared the cardiovascular response to isometric handgrip exercise at 30% between young (mean age 21±0.7) and older men (59±0.8). Similar to our protocol there was a 2 minute contraction phase followed by a four minute relaxation phase. Boutcher and Stocker demonstrated that the older individuals had a smaller increase in heart rate, mean arterial pressure and rate pressure product compared to the younger individuals. They concluded that the reason for the discrepancy between the age groups was a function of a reduced β-adrenergic sensitivity in the older participants (Boutcher & Stocker, 1999). Similarly, Smolander and colleagues (1998) demonstrated an age-related attenuation in the heart rate, to isometric handgrip training at various intensities (20% MVC through 60% MVC) (Smolander et al., 1998). Both the studies by Boutcher and Stocker (1999) and Smolander and colleagues (1998) also demonstrated an age associated attenuation in the rise of blood pressure in response to isometric exercise. In addition to being older, the participants in the current

investigation were also under pharmacologic treatment for hypertension, including β-blockade (n=5). Therefore, the reason for the smaller heart rate and blood pressure increases compared to previous studies (Wiley et al., 1992; Ray et al., 2000) could readily be explained by the effects of aging as well as the pharmacological effects of the anti-hypertensive medications. Despite these differences, the maximal rise in heart rate (10 beats/minute) and blood pressure (MAP 16.2 mmHg) observed at the end of contraction phase 4 were similar to those reported during the initial 2 minute contractions in the studies by Wiley and colleagues (1992) and Ray and Carrasco (2000).

As previously mentioned this was the only study to examine the full cardiovascular response to isometric handgrip training. Direct comparisons between this protocol and others which examined the responses after only a single 2 minute handgrip contraction are not of use, as the current investigation demonstrated a graded response to IHG. For each contraction there was a greater increase in HR, SBP, DBP and RPP which peaked at the end of contraction four. Therefore, any study which utilized a single contraction to estimate the complete response would underestimate the complete response. However, studies which utilized fatiguing contractions may be better at comparing the response as there is an increase in the HR and BP until the force could not longer be maintained (Smolander et al., 1998).

The present study demonstrated that 8-weeks (24 training sessions) of unilateral handgrip training did not attenuate the cardiovascular response to an acute bout of IHG. This is similar to the findings of Ray and Carrasco following five weeks of unilateral IHG (a total of 20 training sessions). These studies demonstrated a slightly attenuated response to an acute bout of IHG with training, but both failed to show significance (p =

0.51, 0.66, 0.21, 0.25, 0.53 for SBP, DBP, HR, RPP and $\dot{Q}$ respectfully). Previous investigations which have utilized rhythmic forearm training have also demonstrated that this form of training does not reduce the acute cardiovascular response. For example, Somers and co-workers found that 30 sessions of repeated forearm contractions at 30% MVC (30/minute) did not alter the acute heart rate (decreases seen in both trained and sham trained limbs) or blood pressure responses, despite a significant attenuation in muscle sympathetic nerve activity (Somers et al., 1992). Contrary to this, Sinoway and colleagues (1996) found that four weeks (5×/week) of rhythmic forearm training (12 contractions/minute at ~30% MVC) attenuated the rise in MAP and muscle sympathetic nerve activity in response to an acute exercise bout. However, in-line with the current investigation and that of Somers and colleagues there was no reduction in training heart rate (Sinoway et al., 1996).

Based on the cardiovascular response seen in the current investigation it can be postulated that the pressor response observed is primarily attributable to vagal withdrawal (Shepherd et al., 1981; Perez-Gonzalez, 1981) The repeated rises seen in HR, BP, and RPP may be attributable to a variety of mechanisms including: an increase in drive from either central command for each contraction, an increase in metabolite buildup, increase in sensitivity and stimulation of muscle afferents, and alteration in the baroreceptor set point following each contraction. None of these mechanisms were investigated in the current study so these conclusions are speculative.

5.2 Aortic stiffness

This study demonstrated that 8-weeks of IHG training did not alter carotid artery stiffness. Our results are in contrast to previous reports which have demonstrated improvements in arterial stiffness with aerobic training. Cross-sectional investigations have shown that regular endurance training is associated with a 20 – 30% increase in arterial compliance in middle aged and older men and women (Tanaka et al., 1998; Tanaka et al., 2000). Subsequent studies have directly examined the effectiveness of aerobic training and shown that arterial stiffness can be reduced in young healthy males (Cameron et al., 1994; Kakiyama et al., 2005), in patients with heart failure (Parnell et al., 2002), and in patients with coronary artery disease (Edwards et al., 2004). In accordance with the results of the current investigation, Ferrier and colleagues demonstrated that aerobic training did not modify systemic arterial compliance in persons with isolated systolic hypertension. Similar to the current protocol, Ferrier and colleagues (2001) had the participants train for 8 weeks. Unlike the current investigation the intervention was 40 minutes of cycle ergometry at 65% of the participants' predetermined maximum heart rate. Following training Ferrier and colleagues did not see any significant improvements in carotid femoral PWV, systemic arterial compliance or aortic impedance. Thus, they concluded that large arterial stiffness associated with isolated systolic hypertension is un-modifiable with aerobic exercise (Ferrier et al., 2001). This could explain why we did not find significant improvements in either measure of aortic, as the present investigation included a population of individuals with isolated systolic hypertension. This later point highlights that the mechanism associated with an improvement in resting arterial blood pressure with IHG is not a result of improved arterial compliance, and therefore the

reduction in arterial blood pressure seen in previous studies (Wiley et al., 1992; Taylor et al., 2003; McGowan et al., 2005a; McGowan et al., 2005b) must be attributable to another mechanism.

5.3 Supine measures

The current investigation demonstrated that 8-weeks of unilateral isometric handgrip exercise did not reduce resting arterial blood pressure. These results are in contrast to previous studies utilizing a similar protocol. Taylor and colleagues demonstrated in a group of medicated and non-medicated hypertensives that 10-weeks of isometric handgrip training reduced resting systolic blood pressure by 19 mmHg and MAP by 11 mmHg (Taylor et al., 2003). Similarly Wiley *et al.* (1992) demonstrated that in people with high normal blood pressure, 8-weeks of isometric handgrip training resulted in a 12 mmHg decrease in SBP. Lastly, using a unilateral training protocol of 4, 3 minute bouts of IHG at 30% of MVC, Ray and Carrasco demonstrated a significant reduction in DBP by 5 mmHg and MAP by 4 mmHg (Ray et al., 2000).

While no significant reduction was observed in SBP or DBP, the reductions seen (4 mmHg and 2 mmHg) are comparable to the reductions observed in the large meta-analyses. The results of meta-analyses which examined aerobic training found an average reduction in SBP of 4.7, 3.4, and 3.8 mmHg and a reductions of 3.1, 2.4, and 2.6 mmHg for DBP (Halbert et al., 1997; Fagard, 2001; Whelton et al., 2002b). The changes seen with resistance training were of 3 mmHg for both systolic and diastolic blood pressures (Kelley et al., 2000). Thus, while the training did not reduce systolic blood pressure with drastic reductions like those seen in the investigations of Wiley and colleagues (1992) and Taylor and colleagues (2003) who both measured blood pressure in the seated

position following 10 minutes of seated rest using a stethoscope and mercury sphygmomanometer, the reductions seen in this investigation are similar to those seen in larger populations using aerobic and resistance training. Furthermore, the reductions seen in BP are likely not a result of acclimatization to the laboratory as all participants were screened and habituated to the laboratory before any measures were made.

No alterations were observed in resting heart rate in accordance with the data from Wiley and colleagues (1992), Ray and Carrasco (2000) and Taylor and colleagues (2003). It is clear that the while the stimulus is significant to reduce resting arterial blood pressure it is insufficient to cause alterations in resting heart rate. With respect to cardiac output as would be expected we did not find any reductions in resting cardiac output. This is likely because reductions seen in arterial blood pressure following chronic training are due to changes in TPR not cardiac output (Pescatello et al., 2004).

5.4 Potential mechanism of reduced blood pressure

One explanation for the improvement seen in resting arterial blood pressure in previous studies could be improved autonomic function. Taylor and colleagues, using power spectral analysis, demonstrated a trend toward an improvement in HR variability and a significant reduction in SBP variability. Thus, they concluded that the reduction in resting arterial blood pressure was in part due to alterations in autonomic nervous system functioning (Taylor et al., 2003). In contrast, Ray and Carrasco did not find alterations in muscle sympathetic nerve activity in a group of normotensive individuals despite a reduction in DBP following 5 weeks of unilateral isometric handgrip training at 30% of MVC (Ray et al., 2000). Somers *et al.* and Sinoway and colleagues demonstrated attenuation in muscle sympathetic nerve activity with rhythmic forearm training (Somers

et al., 1992; Sinoway et al., 1996). It is well established that there is an elevated sympathetic nervous system in hypertension (Abboud, 1982), thus isometric handgrip training may reduce the activity of this system following 8 weeks of training in a population of hypertensives, while no training effect would be observed in young healthy individuals. Thus, direct measures of sympathetic nerve activity need to be measured in our population to determine if training does attenuate this response.

Alterations in endothelial function are one potential mechanism of improved resting arterial blood pressure. Data from our laboratory has shown improvements in endothelial function in persons medicated for hypertension following 8-weeks of bilateral isometric handgrip training, in comparison to a non-exercising control group (McGowan et al., 2005b). The improvements in endothelial function may have contributed to improvements in local arterial blood pressure by allowing the vessel to dilate better in response to local changes in flow. These results using IHG are similar to those seen by Higashi and colleagues (Higashi et al., 1999b). Following 8 weeks of mild aerobic training there were reductions seen in resting SBP and improved endothelial function in patients with essential hypertension. A subsequent study by Higashi and colleagues (Higashi et al., 1999a), further demonstrated that exercise could improve endothelium dependent dilation in patients with mild essential hypertension. Despite these positive results, a recent study by McGowan and colleagues demonstrated that unilateral handgrip training (using the same protocol as this investigation) reduces blood pressure in normotensive individuals but does not improve endothelial function (McGowan et al., 2005a).

Improved baroreflex function has also been suggested as a mechanism of resting arterial blood pressure reduction following IHG training. Kingwell and colleagues, examined the relationship between aortic stiffness and baroreflex functioning. Firstly they observed that compared to normotensive individuals, hypertensive individuals had blunted baroreflex responsiveness compared to normotensive controls as indicated by a 50% reduction in maximum gain, and blunted alterations in HR in response to changes in mean arterial pressure. Similarly they demonstrated that hypertensives had blunted changes in arterial circumference (although this was not significant). Thus, the authors concluded that stiff central arteries are responsible for the blunted response of the baroreceptors (Kingwell, Cameron, Gillies, Jennings, & Dart, 1995). Monahan and colleagues demonstrated that arterial compliance was associated with altered baroreceptor reflex activity (Monahan et al., 2001). Endurance trained older men had more compliant arteries and baroreceptor responses similar to young controls, whereas older sedentary men had stiffer central arteries and blunted baroreceptor responses (Monahan et al., 2001). Interestingly Hunt and colleagues did not observe a close relationship between baroreceptor function and reduced vascular stiffness (Hunt, Farquhar, & Taylor, 2001). They compared beat-to-beat measurements of carotid artery diameter and blood pressure in healthy young and older males both trained and untrained. They found that habitual exercise preserves age related decreases in baroreceptor functioning. More importantly, they determined that decreases in arterial stiffness associated with age may not fully explain changes in baroreflex gain, as neural function predominantly controls baroreflex gain. Furthermore, short term exercise likely improves autonomic function in older adults (Hunt et al., 2001). This further supports the results of

isometric handgrip exercise and the improvements in autonomic function seen by Taylor and colleagues (2003).

Further studies should directly measure baroreceptor functioning following IHG as there may be an improvement in the barorector functioning following training which could potentially be attributed to the acute pressure response during the exercise portion of IHG. Thus the response and functioning of baroreceptors is yet another avenue that needs to be examined as a potential mechanism of attenuated resting arterial blood pressure following training.

One potential mechanism that requires more investigation is alterations in renal blood flow following handgrip training. Momen and colleagues examined renal blood flow velocity during isometric exercise (handgrip at 40% of MVC in groups of younger and older individuals). They found that older individuals had a greater increase in renal vascular resistance towards the end of fatiguing handgrip contraction (Momen, Leuenberger, Handly, & Sinoway, 2004). Perhaps training with static exercise and the repeated rise in renal vascular resistance may alter renal sympathetic nerve activity and hence alter long term blood pressure control.

5.5 Future directions

It could be argued that the lack of a control group is a limitation of the current investigation. However, previous work with isometric handgrip training and the reduction in blood pressure has included control groups (Wiley et al., 1992; Ray et al., 2000; Taylor et al., 2003). The current investigation was a mechanism study aimed at exploring the effectiveness of the training at reducing aortic stiffness, and to identify the acute cardiovascular response to the training. All the participants underwent a detailed and

intense habituation, therefore changes in blood pressure observed were likely as a result of the training not familiarization. Furthermore, this study group included a large intervention group, and based on previous work in this area we had adequate power to detect changes in blood pressure. Therefore, the lack of a control group should not be a concern.

The effectiveness of IHG at reducing resting arterial blood pressure is an area that requires more work as the mechanisms responsible for the reduction in resting arterial blood pressure are still not understood. Specifically, investigations should examine the effectiveness of isometric handgrip training on baroreceptor functioning to examine if the training has an impact on short term blood pressure regulation and if there are acute changes in the baroreceptor set point following training. Moreover, investigations should compare the effectiveness of the different types of IHG protocols to determine which is most effective. Specifically, are the longer contraction periods used by Ray and Carrasco (2000), better than the current protocol; how does the current protocol compare to the bi-lateral training employed by Wiley and colleagues (1992) and Taylor and colleagues (2003). Variations in exercise intensity (%MVC) and work rest phases could be altered. Lastly, further research is required to examine if there is there a beneficial impact of training daily or if thrice weekly training sufficient.

Future studies should also examine the acute effects of handgrip training. As previously described PEH is a common phenomenon following both aerobic and resistance training (MacDonald, 2002). The effectiveness of IHG at causing PEH has yet to be investigated. Whether or not IHG causes PEH or not should be determined. Furthermore, the duration of PEH should be examined. Ambulatory blood pressure

monitoring is another indicator of blood pressure control that could be examined as this would provide insight into whether the training reduces blood pressure over the entire day, including during periods of mild physical activity.

Most importantly, a randomized controlled trial examining the effectiveness of IHG at reducing blood pressure is needed. This will allow a larger population of various at risk individuals to be investigated to determine if the training can prevent the onset of hypertension. A trial such as this could also be used to determine how this form of training compares to pharmacological treatment and/or other forms of exercise.

5.6 Summary and conclusion

Contrary to our hypothesis eight weeks of unilateral handgrip training did not significantly reduce resting arterial blood pressure in a group of pharmacologically treated hypertensive individuals. Despite the lack of significance, systolic blood pressure was reduced by 4 mmHg. As described by Whelton and colleagues even small reductions (3 mmHg) can reduce the rates of stroke and coronary heart disease by 8% and 5% respectively (Whelton et al., 2002a).

In agreement with previous work no training dependent changes were seen in resting heart rate or cardiac output (Taylor et al., 2003; Pescatello et al., 2004). Furthermore, the training did not induce any improvements in aortic stiffness. This is in line with a previous report which demonstrated no improvement in carotid stiffness in a group of aerobically trained individuals with isolated systolic hypertension (Ferrier et al., 2001).

This was the first study to completely examine the cardiovascular response to the complete twenty-four minute protocol. During the fourth contraction the peak heart rate, systolic blood pressure, diastolic blood pressure, and rate pressure product were significantly greater than the response seen during the first contraction. Despite this graded response, the increase in all variables was mild compared to moderate to high intensity aerobic or resistance training. Thus, isometric handgrip training is a safe modality which could be incorporated into a larger exercise program to help reduce blood pressure.

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Appendices

A Study Data

Participant Demographics

	Age	Height (cm)	Weight (kg)	CAD	Meds	Time on Medications (yr)
LJ	59	175.3	88.7	Yes	ACE	4
BM	71	195.6	134.0	No	ACE	15
VP	67	181.6	92.1	Yes	ACE	23
BR	58	165.2	74.8	Yes	ACE,BB	1
LH	64	199.0	90.3	No	Diuretic	5
RE	73	172.7	66.2	No	ACE	4
BS	75	181.6	92.1	Yes	ACE,BB,CCB	2
CB	62	180.3	86.2	No	ACE	8
JD	64	192.0	80.0	Yes	ACE, BB	3
WM	64	177.8	83.9	No	BB	10
BOM	73	182.9	92.5	No	Diuretic	2
MBU	56	186.7	88.0	Yes	ACE, BB	26
DL	69	162.5	72.6	No	ACE, Diuretic	10
EJ	72	167.6	61.2	No	Diuretic	0.25
AS	71	193.0	113.3	Yes	ACE, CCB	8
MP	59	152.4	77.1	No	CCB	7
MBA	72	167.6	65.3	No	ACE	17
AB*	68	177.8	70.3	Yes	ACE,Diuretic	5
LM*	70	152.4	59.0	No	Diuretic	2
HG*	72	174.0	74.0	Yes	ACE, BB, Diuretic	2

*, did not complete study; CAD, coronary artery disease, ACE, angiotensin converting enzyme inhibitor; BB, beta-blocker; CCB, calcium channel blocker

Supine data

	SBP		DBP		MAP		HR		$\dot{Q}$	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
LJ	122.67	119.00	60.00	66.00	80.89	83.67	49.84	50.07	4.20	3.60
BM	127.67	115.00	79.67	69.33	95.67	84.56	57.51	66.19	7.18	7.60
VP	145.33	122.67	82.00	69.00	103.11	86.89	61.13	54.52	2.30	2.01
BR	124.00	124.33	82.33	88.33	96.22	100.33	61.46	57.03	2.61	2.95
LH	117.00	127.00	53.00	61.33	74.33	83.22	53.22	58.54	3.26	7.50
RE	131.67	121.33	70.00	67.67	90.56	85.56	46.12	47.44	4.82	6.26
BS	118.33	123.33	64.67	56.00	82.56	78.44	42.09	41.38	4.50	2.83
CB	132.67	135.67	83.33	89.67	99.78	105.00	67.24	62.02	3.76	3.71
WM	105.67	105.67	66.33	61.67	79.44	76.33	54.46	52.27	4.18	3.07
JD	117.33	111.33	68.67	64.00	84.89	79.78	47.70	47.57	5.71	5.41
MP	113.00	115.00	63.67	64.67	80.11	81.44	56.60	60.53	2.47	6.46
DL	113.67	110.00	72.33	68.33	86.11	82.22	58.52	49.07	4.17	3.40
BOMO	136.00	123.67	76.67	72.67	96.44	89.67	56.84	50.12	4.85	5.53
AS	124.67	137.33	67.00	77.00	86.22	97.11	52.48	58.47	5.99	6.22
MBA	136.67	118.67	83.00	69.67	100.89	86.00	83.37	71.25	6.00	4.06
MBU	136.67	139.33	74.00	73.67	94.89	95.56	50.96	51.28	4.86	6.32
EJ	127.67	114.33	76.00	67.33	93.22	83.00	54.11	53.45	na	na
average	125.33	121.39	71.92	69.78	89.73	86.99	56.10	54.78	4.43	4.81
SEM	2.53	2.31	2.15	2.13	2.08	1.94	2.26	1.82	0.34	0.45

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, Heart rate; $\dot{Q}$, Cardiac output; na, not available; SEM, standard error of mean.

Aortic Stiffness

	CAPP		Distensibility		Stiffness Index		Pre		Post	
	PRE	POST	PRE	POST	PRE	POST	Sd	Dd	Sd	Dd
LH	55.54	54.75	0.00245	0.00053	3.37	4.79	4.42	4.15	4.25	4.18
BR	35.42	32.90	0.00537	0.00622	2.79	2.67	3.30	3.03	3.38	3.08
RE	63.77	52.28	0.00269	0.00258	3.05	3.32	3.31	3.05	3.29	3.09
VP	36.25	40.08	0.00161	0.00447	3.92	2.89	3.70	3.59	3.40	3.13
LJ	48.63	51.40	0.00275	0.00233	3.28	3.35	2.52	2.37	2.58	2.44
BS	42.12	40.40	0.00277	0.00168	3.43	3.85	3.05	2.88	3.09	2.99
JD	39.91	34.32	0.00438	0.00551	2.94	2.82	3.27	3.02	3.28	3.01
WM	35.43	41.81	0.00408	0.00614	3.11	2.60	3.12	2.92	3.12	2.78
CB	55.54	35.46	0.00245	0.00459	3.37	2.89	3.25	3.04	3.23	2.99
MP	47.66	47.92	0.00151	0.00149	4.00	3.85	2.87	2.77	2.86	2.76
DL	35.50	32.08	0.00196	0.00269	3.80	3.52	3.13	3.03	3.13	3.00
MBU	53.67	57.24	0.00303	0.00302	3.11	3.05	2.76	2.56	2.78	2.57
BOMO	43.91	57.24	0.00372	0.00302	2.96	3.05	3.07	2.84	3.06	2.84
AS	29.71	28.14	0.00459	0.00603	3.10	2.84	3.06	2.87	3.08	2.84
MBA	33.70	36.40	0.00255	0.00250	3.52	3.55	2.83	2.72	2.85	2.72
EJ	na	na	na	na	na	na	na	na	na	na
BM	na	na	na	na	na	na	na	na	na	na
Mean	43.79	42.83	0.00306	0.00352	3.32	3.27				
SEM	2.58	2.54	0.00029	0.00048	0.09	0.15				

CAPP, carotid artery pulse pressure, Sd, systolic diameter; Dd, diastolic diameter; SEM, standard error of the mean; na, not available.

Aortic root diameters

	Pre		Post	
	Sd	Dd	Sd	Dd
LJ	2.02	1.99	2.02	1.89
VP	2.20	2.09	2.24	2.11
BR	1.94	1.79	2.02	1.79
RE	2.37	2.15	2.37	2.07
BS	2.10	1.91	2.12	1.85
JD	2.05	1.85	2.04	1.84
WM	2.53	2.26	2.51	2.25
MP	2.24	1.84	2.20	1.83
AS	2.37	2.26	2.46	2.27
MBA	2.21	2.02	2.24	2.00
CB	2.25	2.01	2.20	2.00
MBU	2.29	1.99	2.25	1.89
BOMO	2.28	2.03	2.27	2.00
DL	2.21	2.12	2.21	2.04
BM	2.32	2.20	2.49	2.11
LH	2.41	2.26	2.38	2.28
average	2.24	2.05	2.25	2.01
SEM	0.04	0.04	0.04	0.04
ARD	2.11		2.09	
	0.04		0.04	

Sd, systolic diameter; Dd, diastolic diameter; SEM, standard error of mean; ARD, aortic root diameter;

Aortic area reproducibility

	Pre		Reproducibility				Difference (day 1 - day 2)	
	Sa	Da	Sa	Da	CV Sa	CV Da	Sd	Dd
LJ	4.9876	4.3991	5.1311	4.3669	2.0059	0.5188	-0.1435	0.0322
LH	15.3439	13.5048	14.3760	13.5265	4.6053	0.1136	0.9678	-0.0217
VP	10.7231	10.1317	8.7485	7.7314	14.3414	19.0031	1.9746	2.4003
BR	8.5530	7.1869	8.9197	7.4775	2.9680	2.8027	-0.3667	-0.2906
RE	8.5841	7.3253	8.7325	7.4829	1.2115	1.5046	-0.1483	-0.1575
BS	7.2934	6.5302	7.6073	7.0686	2.9793	5.5984	-0.3139	-0.5383
JD	8.4096	7.1579	8.4267	7.1526	0.1440	0.0521	-0.0171	0.0053
MP	6.4542	6.0214	6.3347	5.9901	1.3217	0.3694	0.1195	0.0314
AS	7.3622	6.4793	7.3729	6.5850	0.1026	1.1442	-0.0107	-0.1057
MBA	6.3001	5.8012	6.3050	5.7728	0.0555	0.3473	-0.0049	0.0284
CB	8.2703	7.2504	8.4554	7.2530	1.5650	0.0259	-0.1851	-0.0027
						grand mean	8.2983	7.3846
						Standard deviation	0.6958	0.7747
						CV	**Error Method**	
						2.85	**2.86**	**0.08**	**0.10**

Sa, systolic area; Da, diastolic area; CV, coefficient of variation

Aortic area change reproducibility

	PRE			REPRO				
	Sa	Da	□AREA	Sa	Da	□AREA	CV	Difference (day 1 - day 2)
LJ	4.9876	4.3991	0.5885	5.1311	4.3669	0.7642	18.3675	-0.1757
LH	15.3439	13.5048	1.8391	14.3760	13.5265	0.8495	52.0507	0.9895
VP	10.7231	10.1317	0.5914	8.7485	7.7314	1.0171	37.4308	-0.4257
BR	8.5530	7.1869	1.3661	8.9197	7.4775	1.4422	3.8314	-0.0761
RE	8.5841	7.3253	1.2588	8.7325	7.4829	1.2496	0.5186	0.0092
BS	7.2934	6.5302	0.7631	7.6073	7.0686	0.5387	24.3786	0.2244
JD	8.4096	7.1579	1.2517	8.4267	7.1526	1.2741	1.2547	-0.0224
MP	6.4542	6.0214	0.4328	6.3347	5.9901	0.3446	16.0355	0.0881
AS	7.3622	6.4793	0.8829	7.3729	6.5850	0.7879	8.0419	0.0950
MBA	6.3001	5.8012	0.4989	6.3050	5.7728	0.5322	4.5769	-0.0334
CB	8.2703	7.2504	1.0199	8.4554	7.2530	1.2023	11.6105	-0.1824
							grand mean	0.9316
							standard deviation	0.3574
							CV	**Error Method**
							16.19	**0.38**

Sa, systolic area; Da, diastolic area; CV, coefficient of variation

Final 10 seconds of Systolic blood pressure

	Pre					Post				
	RST	CX1	CX2	CX3	CX4	RST	CX1	CX2	CX3	CX4
BS	150.91	133.68	142.19	164.48	163.12	148.19	163.70	136.21	172.75	168.68
VP	137.97	143.83	168.63	153.54	225.65	123.80	155.90	143.21	141.37	146.39
BR	137.97	129.79	140.70	135.62	157.73	138.54	131.02	105.55	97.53	167.34
LJ	138.82	140.54	130.49	142.16	118.88	140.12	118.75	117.87	129.67	182.94
WM	119.53	123.50	113.51	123.22	122.47	141.68	152.29	156.18	154.32	152.26
CB	136.38	152.46	149.75	144.44	149.94	146.38	149.93	142.93	117.31	98.79
JD	141.45	133.48	140.21	140.31	141.80	130.31	142.19	153.65	151.74	148.60
MBU	147.16	160.86	149.98	182.48	173.83	150.84	187.90	172.00	180.05	173.47
DL	126.31	167.40	166.21	170.59	179.37	117.97	133.38	134.52	139.09	142.88
EJ	154.86	145.91	141.67	151.98	148.16	124.10	117.63	115.82	104.37	124.43
AS	130.72	159.40	168.69	156.70	165.89	143.68	161.62	158.64	169.16	185.52
MP	128.87	129.52	126.40	135.88	157.91	101.17	135.06	133.02	130.56	131.69
BOMO	159.45	143.75	177.79	176.06	175.60	149.12	163.59	158.73	160.73	181.14
MEAN	139.26	143.39	147.40	152.11	160.03	135.07	147.15	140.64	142.20	154.16
SEM	3.21	3.76	5.20	4.86	7.53	4.09	5.56	5.39	7.17	7.15

RST, rest; CX, contraction; SEM, standard error of mean

Final 10 seconds of Diastolic blood pressure

	Pre					Post				
	RST	CX1	CX2	CX3	CX4	RST	CX1	CX2	CX3	CX4
BS	75.64	65.47	66.37	81.18	82.49	70.44	70.21	59.86	74.01	80.05
VP	83.25	88.01	105.42	98.56	139.64	74.95	89.13	87.07	96.76	106.31
BR	87.20	65.98	89.19	88.02	97.24	108.76	100.22	89.71	85.80	107.18
LJ	74.19	87.04	71.63	88.04	72.77	78.49	63.13	76.10	80.70	109.35
WM	74.76	76.33	72.13	79.13	79.23	89.40	92.50	94.32	86.52	87.30
CB	77.73	90.58	87.62	85.31	88.99	87.78	87.97	86.66	76.07	65.96
JD	85.09	67.06	69.86	71.65	74.80	78.75	87.42	97.97	94.38	101.49
MBU	87.92	98.19	95.99	106.30	106.68	87.37	105.77	97.73	101.82	97.32
DL	68.73	97.71	98.29	100.71	101.45	63.15	71.34	70.23	71.82	74.53
EJ	87.82	81.75	78.40	81.34	81.03	69.66	64.35	60.61	62.50	71.71
AS	61.78	105.26	102.11	94.93	101.48	81.98	89.69	88.34	89.03	101.65
MP	65.80	80.29	82.64	90.27	106.08	47.08	82.76	81.97	76.93	77.14
BOMO	89.98	85.88	104.32	101.81	96.92	83.77	91.69	80.37	89.64	103.93
MEAN	77.49	83.64	84.97	88.79	94.32	78.15	83.71	82.55	83.03	90.00
SEM	2.48	3.68	3.74	2.77	5.20	4.25	3.80	3.66	3.18	4.33

RST, rest; CX, contraction; SEM, standard error of mean

Final 10 seconds of heart rate

	Pre					Post				
	RST	CX1	CX2	CX3	CX4	RST	CX1	CX2	CX3	CX4
BS	45.31	44.92	52.17	53.02	55.23	37.11	43.63	43.93	49.01	41.31
VP	48.17	61.95	66.02	63.94	67.49	55.47	67.34	66.90	72.70	86.37
BR	60.04	66.37	75.04	68.17	72.72	59.94	70.30	70.54	73.60	81.56
LJ	46.28	52.15	54.35	55.81	54.66	50.15	57.64	55.82	58.26	61.95
WM	54.36	59.63	59.94	64.40	66.08	52.33	55.26	55.35	55.87	56.67
CB	72.39	82.98	83.42	82.11	84.23	62.02	68.75	69.69	67.95	70.76
JD	45.79	55.97	54.11	55.91	61.78	47.25	50.38	54.40	53.87	55.52
MBU	55.86	70.74	76.73	77.18	83.68	54.70	62.33	58.24	62.03	59.27
DL	56.00	59.60	62.26	64.02	67.00	49.45	55.48	57.84	54.51	57.95
EJ	51.95	54.93	52.73	53.90	54.42	54.30	53.85	53.67	55.08	56.04
AS	51.86	65.16	61.08	63.78	61.93	57.53	61.00	60.32	61.44	61.21
MP	63.59	67.26	69.69	74.18	78.02	63.71	64.71	66.68	66.67	69.63
BOMO	55.97	59.86	59.66	61.44	62.93	49.97	53.42	50.40	50.42	53.34
RE	45.34	48.95	52.65	48.69	49.03	47.73	55.37	53.12	52.21	54.39
MBA	86.70	90.32	92.84	94.26	96.41	75.04	93.00	85.31	86.09	90.60
Mean	55.97	62.72	64.85	65.39	67.71	54.45	60.83	60.15	61.31	63.77
SEM	2.94	3.11	3.20	3.17	3.40	2.26	2.97	2.63	2.67	3.50

RST, rest; CX, contraction; SEM, standard error of mean

Final 10 seconds of rate-pressure-product

	Pre					Post				
	RST	CX1	CX2	CX3	CX4	RST	CX1	CX2	CX3	CX4
BS	6837.41	6003.01	7415.16	8723.18	9002.51	5499.49	7143.03	5979.15	8477.30	6969.36
VP	6646.04	8910.35	11133.45	9814.36	15229.67	6866.87	10499.20	9590.86	10276.33	12643.14
BR	8284.03	8614.87	10558.51	9245.08	11470.04	8303.75	9207.44	7445.06	7178.67	13647.75
LJ	6426.95	7329.95	7098.79	7933.49	6498.20	7026.54	6844.97	6580.28	7555.24	11330.66
WM	6496.93	7364.05	6803.61	7934.39	8093.98	7413.23	8414.81	8644.43	8621.87	8628.71
CB	9872.42	12651.43	12490.68	11860.36	12629.10	9078.82	10307.96	9960.41	7970.36	6989.70
JD	6477.83	7471.26	7587.11	7845.95	8760.37	6157.19	7162.85	8360.82	8174.66	8250.72
MBU	8218.10	11370.27	11508.04	14086.73	14543.48	8249.74	11711.29	10018.90	11169.01	10281.76
DL	7071.74	9977.03	10347.15	10921.18	12017.94	5833.22	7398.58	7780.55	7572.39	8279.12
EJ	8044.62	8014.03	7469.30	8190.76	8062.85	6739.25	6334.51	6216.45	5749.19	6973.55
AS	6776.85	10385.92	10303.12	9993.40	10274.06	8266.53	9859.05	9569.68	10392.98	11355.87
MP	8193.96	8711.78	8806.46	10081.55	12321.38	6446.62	8739.95	8869.63	8705.16	9169.61
BOMO	8926.41	8604.53	10606.94	10818.00	11050.18	7450.51	8741.27	8001.21	8104.37	9662.51
Mean	7559.48	8877.58	9394.49	9803.73	10765.67	7179.37	8643.45	8232.11	8457.50	9552.50
SEM	305.95	505.00	536.22	505.55	726.17	298.06	453.28	385.24	404.34	607.06

RST, rest; CX, contraction; SEM, standard error of mean

Cardiac output

Pre

PRE	seated rest	End CXN 1	Start rest 1	end CXN 2	Start rest 2	end CXN 3	start rest 3	End CXN 4	start rest 4
LJ	3.82	4.24	4.93	2.99	4.02	3.62	4.20	2.67	3.10
VP	1.80	2.06	2.41	2.32	3.02	2.24	3.04	3.15	3.77
BR	1.80	3.11	3.23	4.89	4.90	5.44	6.31	4.18	4.22
RE	5.47	4.39	5.47	4.09	4.32	2.19	2.01	2.06	3.47
BS	3.14	1.73	2.35	2.33	2.08	2.52	2.28	2.24	2.45
JD	2.55	3.82	3.94	4.55	3.12	4.20	4.03	3.84	4.57
WM	2.19	2.37	2.30	2.40	2.28	2.55	2.49	2.61	2.38
MP	3.26	4.24	4.80	4.06	4.25	3.71	3.96	3.84	3.85
AS	6.09	4.54	6.20	9.01	10.78	9.53	7.39	5.43	7.32
MBA	4.30	4.73	4.96	4.88	5.30	5.77	5.44	5.42	4.65
CB	4.01	5.81	6.37	7.17	5.84	6.34	6.11	5.74	6.53
MBU	3.75	3.97	4.94	5.77	5.98	5.68	5.04	7.02	8.08
BOMO	2.44	9.27	4.12	4.36	7.22	3.81	4.35	3.88	4.99
DL	4.43	4.44	3.77	3.97	4.16	3.50	4.21	4.55	3.72
Mean	3.50	4.20	4.27	4.48	4.81	4.36	4.35	4.04	4.51
SEM	0.36	0.51	0.37	0.52	0.62	0.56	0.44	0.41	0.48

CXN, contraction; SEM, standard error of mean

Post

	seated rest	end CXN 1	Start rest 1	end CXN 2	Start rest 2	end CXN 3	start rest 3	End CXN 4	start rest 4
LJ	2.63	2.38	2.70	2.30	2.41	2.69	3.20	2.23	3.16
VP	2.47	1.98	2.47	2.20	2.89	3.37	3.46	4.59	2.93
BR	2.87	2.51	3.22	3.73	3.37	3.33	3.27	3.04	4.08
RE	3.28	3.46	6.64	3.63	4.79	3.54	4.25	3.75	4.30
BS	2.53	1.67	2.09	2.83	2.66	3.14	2.95	3.81	3.99
JD	3.16	2.93	3.29	4.49	4.42	4.98	5.88	3.53	5.71
WM	4.69	5.91	4.65	5.19	4.06	4.28	4.95	4.41	5.24
MP	3.72	3.70	4.44	4.48	4.59	4.27	3.98	4.32	5.05
AS	5.86	6.99	7.10	6.02	7.27	8.23	7.83	8.84	8.54
MBA	3.58	4.24	4.41	3.36	4.08	3.92	4.52	4.70	5.45
CB	3.28	3.49	3.21	3.95	3.93	4.05	3.58	4.27	3.76
MBU	4.53	5.13	5.32	5.79	6.35	5.18	7.43	5.06	5.52
BOMO	2.38	2.78	3.12	2.45	2.74	1.98	3.58	2.54	3.21
DL	2.32	2.66	2.94	3.07	2.70	4.17	3.51	3.49	3.63
Mean	3.38	3.56	3.97	3.82	4.02	4.08	4.46	4.19	4.61
SEM	0.29	0.43	0.42	0.34	0.40	0.41	0.43	0.44	0.41

CXN, contraction; SEM, standard error of mean

B Statistical Tables

Supine Data – Repeated measures ANOVA (Pre-Post)

Systolic blood pressure

	SS	df	MS	F	p
Intercept	537126.1	1	537126.1	2743.102	0.000000
Error	3328.8	17	195.8		
TIME	128.4	1	128.4	2.822	0.111266
Error	773.8	17	45.5		

Diastolic blood pressure

	SS	df	MS	F	p
Intercept	189515.1	1	189515.1	844.2759	0.000000
Error	3816.0	17	224.5		
TIME	38.7	1	38.7	1.4774	0.240799
Error	445.5	17	26.2		

Mean arterial pressure

	SS	df	MS	F	p
Intercept	285710.0	1	285710.0	2373.473	0.000000
Error	2046.4	17	120.4		
TIME	62.8	1	62.8	2.183	0.157866
Error	489.3	17	28.8		

Heart rate

	SS	df	MS	F	p
Intercept	121091.6	1	121091.6	340.3862	0.000000
Error	6047.7	17	355.7		
TIME	15.3	1	15.3	1.0294	0.324523
Error	252.3	17	14.8		

Cardiac output

	SS	df	MS	F	p
Intercept	3619.60	1	3619.603	3.267975	0.089481
Error	17721.57	16	1107.598		
TIME	0.77	1	0.765	0.517059	0.482470
Error	23.68	16	1.480		

Aortic Stiffness – Repeated measures ANOVA (Pre-Post)

Carotid artery pulse pressure

	SS	df	MS	F	p
Intercept	56264.79	1	56264.79	337.4185	0.000000
Error	2334.51	14	166.75		
TIME	6.87	1	6.87	0.2295	0.639278
Error	418.83	14	29.92		

Distensibility

	SS	df	MS	F	p
Intercept	0.000325	1	0.000325	85.23850	0.000000
Error	0.000053	14	0.000004		
TIME	0.000002	1	0.000002	1.83424	0.197084
Error	0.000012	14	0.000001		

Stiffness Index

	SS	df	MS	F	p
Intercept	325.4904	1	325.4904	992.3059	0.000000
Error	4.5922	14	0.3280		
TIME	0.0156	1	0.0156	0.1090	0.746189
Error	1.9981	14	0.1427		

Cardiovascular Response – 2-way repeated measures ANOVA (Phase × Time)

Systolic blood pressure

	SS	Df	MS	F	p
Intercept	2776488	1	2776488	2294.001	0.000000
TIME	686	1	686	0.567	0.458956
Error	29048	24	1210		
PHASE	5379	4	1345	6.626	0.000094 *
PHASE*TIME	679	4	170	0.836	0.505367
Error	19480	96	203		

Post hoc – Tukey's HSD for Phase

	PHASE	1	2	3	4	5
1	REST		0.249588	0.417530	0.092663	0.000134 *
2	CXN1	0.249588		0.997827	0.989306	0.028421 *
3	CXN2	0.417530	0.997827		0.931779	0.011361 *
4	CXN3	0.092663	0.989306	0.931779		0.095808
5	CXN4	0.000134 *	0.028421 *	0.011361 *	0.095808	

Diastolic blood pressure

	SS	Df	MS	F	p
Intercept	945727.1	1	945727.1	1777.405	0.000000
TIME	224.5	1	224.5	0.422	0.522111
Error	12770.0	24	532.1		
PHASE	2765.5	4	691.4	7.632	0.000022 *
PHASE*TIME	216.9	4	54.2	0.598	0.664619
Error	8696.7	96	90.6		

Post hoc – Tukey's HSD for PHASE

	PHASE	1	2	3	4	5
1	REST		0.228091	0.175722	0.021898 *	0.000120 *
2	CXN1	0.228091		0.999934	0.861940	0.011411 *
3	CXN2	0.175722	0.999934		0.914208	0.016978 *
4	CXN3	0.021898 *	0.861940	0.914208		0.146405
5	CXN4	0.000120 *	0.011411 *	0.016978 *	0.146405	

Heart rate

	SS	Df	MS	F	p
Intercept	571305.2	1	571305.2	896.9834	0.000000
TIME	390.0	1	390.0	0.6123	0.440483
Error	17833.7	28	636.9		
PHASE	1853.7	4	463.4	45.2307	0.000000 *
PHASE*TIME	60.4	4	15.1	1.4750	0.214531
Error	1147.5	112	10.2		

Post hoc – Tukey's HSD for PHASE

	PHASE	1	2	3	4	5
1	REST		0.000114 *	0.000114 *	0.000114 *	0.000114 *
2	CXN1	0.000114 *		0.906275	0.320227	0.000157 *
3	CXN2	0.000114 *	0.906275		0.839537	0.001522 *
4	CXN3	0.000114 *	0.320227	0.839537		0.036678 *
5	CXN4	0.000114 *	0.000157 *	0.001522 *	0.036678 *	

Rate pressure product

	SS	Df	MS	F	p
Intercept	1.017407E+10	1	1.017407E+10	975.1294	0.000000
TIME	2.444132E+07	1	2.444132E+07	2.3426	0.138958
Error	2.504055E+08	24	1.043356E+07		
PHASE	1.038401E+08	4	2.596002E+07	20.2572	0.000000 *
PHASE*TIME	6.983143E+06	4	1.745786E+06	1.3623	0.252797
Error	1.230263E+08	96	1.281524E+06		

Post hoc – Tukey's HSD for PHASE

	PHASE	1	2	3	4	5
1	REST		0.000338 *	0.000230 *	0.000118 *	0.000117 *
2	CXN1	0.000338 *		0.999839	0.763495	0.000319 *
3	CXN2	0.000230 *	0.999839		0.849971	0.000519 *
4	CXN3	0.000118 *	0.763495	0.849971		0.012574 *
5	CXN4	0.000117 *	0.000319 *	0.000519 *	0.012574 *	

Cardiac output

	SS	Df	MS	F	p
Intercept	4184.797	1	4184.797	261.9516	0.000000
TIME	2.850	1	2.850	0.1784	0.676200
Error	415.362	26	15.975		
PHASE	25.105	8	3.138	4.2641	0.000092 *
PHASE*TIME	5.148	8	0.644	0.8745	0.538866
Error	153.074	208	0.736		

Post hoc – Tukey's HSD for PHASE

	PHASE	1	2	3	4	5	6	7	8	9
1	seated rest		0.6471	0.0922	0.0633	0.0013 *	0.0260 *	0.0015 *	0.0979	0.0001 *
2	END CXN 1	0.6471		0.9827	0.9629	0.3594	0.8740	0.3882	0.9850	0.0888
3	Start RST 1	0.0922	0.9827		1.0000	0.9481	1.0000	0.9582	1.0000	0.6375
4	End CXN 2	0.0633	0.9629	1.0000		0.9740	1.0000	0.9800	1.0000	0.7280
5	Start RST 2	0.0013 *	0.3594	0.9481	0.9740		0.9966	1.0000	0.9424	0.9995
6	End CXN 3	0.0260 *	0.8740	1.0000	1.0000	0.9966		0.9977	1.0000	0.8827
7	Start RST 3	0.0015 *	0.3882	0.9582	0.9800	1.0000	0.9977		0.9533	0.9991
8	End CXN 4	0.0979	0.9850	1.0000	1.0000	0.9424	1.0000	0.9533		0.6217
9	Start RST 4	0.0001 *	0.0888	0.6375	0.7280	0.9995	0.8827	0.9991	0.6217	