The Effect of Isometric Muscular Contractions on Blood Pressure and Arterial Distensibility

THE EFFECT OF ISOMETRIC HANDGRIP AND ISOMETRIC LEG MUSCULAR CONTRACTIONS ON RESTING BLOOD PRESSURE AND ARTERIAL DISTENSIBILITY IN PERSONS MEDICATED FOR HYPERTENSION

By

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ABSTRACT

Hypertension and reduced arterial distensibility are independent risk factors for cardiovascular disease. Previous research has found that isometric training reduces resting blood pressure (RBP) (Wiley et al. 1992; Taylor et al. 2003) yet the mechanisms responsible remain elusive. Improved arterial distensibility may contribute to this reduction in RBP. The purpose of the present study was threefold: 1) to replicate the RBP lowering effect of isometric handgrip (IHG) exercise; 2) to compare IHG and isometric leg press (ILP) based in their RBP lowering effects; and 3) to determine if central or peripheral arterial distensibility improved with IHG or ILP. The population examined was people whom were medicated for hypertension.

RBP, as assessed by brachial oscillometry, and arterial distensibility, as assessed by Doppler ultrasound and applanation tonometry in the carotid, brachial and femoral arteries, were measured pre training, after 4 weeks of training, and post training. Participants performed unilateral IHG exercise (n=10) or ILP exercise (n=9) 3 times/week for 8 weeks at 30% MVC or acted as a non-exercising control group (n=5).

Results indicated that the present study was unable to reproducethe RBP reductions noted in previous studies using IHG exercise. Also, the ILP exercise group did not experience reductions in RBP. Finally, neither central nor peripheral arterial distensibility improved in the IHG or ILP group when compared to the control group.

Although these findings are contrary to our hypotheses one must consider that the control group examined contained very few subjects. This may have limited our ability to detect statistically significant changes in RBP and arterial distensibility.

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LIST OF ABBREVIATIONS

ACE	angiotensin converting enzyme
ANOVA	analysis of variance
BP	blood pressure
C	control group
CV	coefficient of variation
CVD	cardiovascular disease
DBP	diastolic blood pressure
ECG	electrocardiogram
HR	heart rate
IHG	isometric handgrip
ILP	isometric leg press
MAP	mean arterial pressure
mmHg	millimeters of mercury
MSNA	muscle sympathetic nerve activity
MVC	maximal voluntary contraction
NO	nitric oxide
PEH	post exercise hypotension
PP	pulse pressure
RAA	renin angiotensin aldosterone
SBP	systolic blood pressure
SEM	standard error of the mean
Tukey HSD	Tukey honestly significant difference
VO_{2max}	maximal oxygen uptake
1RM	one repetition maximum

1.0 INTRODUCTION AND HYPOTHESIS

1.1 Introduction

Hypertension is considered one of the quintessential risk factors for cardiovascular disease (CVD). More specifically, hypertension plays a key etiologic role in the development of ischemic or coronary heart disease, cerebrovascular disease, cardiac and renal failure (WHO, 2003; Kannel, 1996).

Blood pressure (BP) is regulated by feedback control systems that rely on autonomic nerves and circulating hormones as their effector mechanisms. Also, local factors, including endothelial factors and metabolites contribute to BP regulation. These systems control BP by adjusting heart rate (HR), stroke volume, systemic vascular resistance, and blood volume (Dampney et al., 2002).

Due to increasing longevity and the prevalence of unhealthy lifestyles, hypertension is becoming a common health problem. The goal of hypertension management is to reduce morbidity and mortality by the least intrusive means possible. In addition to pharmacological interventions, the adoption of a healthy lifestyle is an effective treatment strategy for hypertension. Numerous modifiable risk factors, including obesity, physical inactivity, high dietary salt intake, stress, and high alcohol consumption, are associated with the development and progression of hypertension (WHO, 2003). Therefore, if these factors can be targeted by treatment strategies, high BP is eminently preventable.

Physical activity in particular is inversely associated with morbidity and mortality from CVD (Blair et al., 1989) and has been shown to have a beneficial effect on BP

(Whelton, Chin, Xin, & He, 2002). Currently, it is recommended that individuals accumulate 30 minutes or more of moderate-intensity aerobic activity on most, preferably all, days of the week (Pescatello et al., 2004). The evidence supporting resistance training as a form of exercise that may lower BP is equivocal at this time but appears promising (Pescatello et al., 2004). One form of exercise that has recently been receiving attention is isometric exercise.

Kiveloff and Huber (1971) offered the first evidence of a hypotensive effect following iosmetric training 30 years ago. Since this time, a number of randomized controlled trials have confirmed that isometric exercise does lower resting blood pressure. Wiley et al. studied individuals with high-normal BP before and after 8 weeks of isometric handgrip (IHG) exercise. They noted reductions in systolic blood pressure (SBP) (from 134.1 to 121.4 mmHg) and diastolic blood pressure (DBP) (from 86.5 to 71.6 mmHg) (Wiley, Dunn, Cox, Hueppchen, & Scott, 1992). Perhaps of more clinical importance, the effect of IHG was studied in an elderly population with hypertension (Taylor, McCartney, Kamath, & Wiley, 2003). Following 10 weeks of training, significant reductions in SBP and mean arterial pressure (MAP) were documented.

A direct relationship exists between the size of the active muscle mass and the magnitude of the increase in mean arterial blood pressure, even when contractions are performed at the same relative intensity (Seals, Washburn, Hanson, Painter, & Nagle, 1983). Therefore, if an IHG contraction at 30% MVC elicits a given pressor response then an isometric leg press (ILP) contraction at 30% MVC would be assumed to elicit an

even greater response. Perhaps a greater reduction in resting BP will follow isometric exercise with a larger muscle mass.

Although a few studies have attempted to pinpoint the mechanisms responsible for the BP lowering effect of isometric exercise, no conclusions have been made in the literature. It has been speculated that decreases in sympathetic nerve activity (Ray & Carrasco, 2000; Sinoway et al., 1996; Somers, Leo, Shields, Clary, & Mark, 1992), improved endothelial function (Sherman, 2000; Sinoway et al., 1987), and baroreceptor resetting (Hunt, Farquhar, & Taylor, 2001; Monahan, Tanaka, Dinenno, & Seals, 2001) may underlie the reduction in BP. Also, an increase in arterial distensibility may be one of the mechanisms responsible (Tanaka et al., 2000).

Arterial distensibilty is a measure of an artery's ability to expand and contract with cardiac pulsation and relaxation. Arteries principally function as "cushions" whereby they dampen the pressure oscillations resulting from intermittent ventricular ejection via their distensible nature (Safar, Laurent, Pannier, & London, 1987). In addition to its undesirable impact on BP, reduced arterial distensibility is now recognized as an independent risk factor for CVD (Arnett, Evans, & Riley, 1994). Aging and hypertension are considered the most common factors contributing to arterial stiffness.

Following a number of cross-sectional and interventional studies, it seems that regular aerobic exercise has the ability to prevent and even reverse the central arterial stiffening seen in the aged (Cameron & Dart, 1994; Schmidt-Trucksass et al., 1999; Tanaka, DeSouza, & Seals, 1998; Tanaka et al., 2000; Vaitkevicius et al., 1993). Resistance training however does not appear to beneficially modify central or peripheral

arterial distensibility (Bertovic et al., 1999; Miyachi et al., 2003). In fact, resistance training may exacerbate the age associated increases in arterial stiffening. The impact of isometric exercise on central and peripheral arterial distensibility remains to be studied. Given the impressive BP reductions that follow isometric training, investigation of arterial distensibility is warranted.

1.2 Summary and Hypothesis

Isometric exercise has been proven to reduce resting BP in young healthy individuals (Ray et al., 2000; Wiley et al., 1992) as well as in older adults with hypertension (Taylor et al., 2003). All of the randomized controlled studies that have demonstrated a reduction in BP have used IHG. Due to the increased pressor response that accompanies exercise with a larger muscles mass, BP reductions following ILP need to be examined. Although speculations have been made, the mechanism responsible for the BP reduction following IHG remains elusive.

The purpose of the present study was threefold: 1) to reproduce the BP lowering effect of IHG training in persons medicated for hypertension, 2) to compare IHG and isometric leg press (ILP) with respect to their BP lowering effects, and 3) to determine if IHG of ILP modify central and/or peripheral arterial distensibility.

2.0 REVIEW OF LITERATURE

2.1 Blood Pressure Regulation

Numerous interconnected systems control blood pressure by adjusting (HR), stroke volume (SV), systemic vascular resistance, and blood volume. These regulatory feedback control systems rely on autonomic nerves and circulating hormones as their effector mechanisms. Also, local factors, including endothelial factors and metabolites contribute to BP regulation (Dampney et al., 2002).

2.1.1 Neural regulation

Regulation of BP by the nervous system depends on receptors in the periphery that provide input to the cardiovascular center. The cardiovascular center, located in the medulla oblongata, transmits both parasympathetic and sympathetic impulses to the heart and blood vessels. Parasympathetic stimulation of the heart, via the vagus nerve, acts to decrease HR. Sympathetic impulses are transmitted through the spinal cord to peripheral nerves innervating the heart, which results in increased HR and cardiac contractility, while sympathetic stimulation of the smooth muscle in blood vessels results in vasoconstriction (Guyton & Hall, 1996).

The peripheral receptors that prompt the cardiovascular center to send either sympathetic or parasympathetic impulses, for the most part, operate as negative feedback reflex systems. The two main receptors responsible for blood pressure regulation are baroreceptors and chemoreceptors.

The arterial baroreceptors sense systemic blood pressure indirectly by the extent of stretch of the receptors in the walls of the carotid sinus and aortic arch. Alterations in

the arterial baroreceptor afferent discharge transmitted to the central nervous system cause reflex adjustments that oppose the changes in BP. For example, a fall in BP (less stretch) reduces afferent baroreceptor discharge and triggers a reflex increase in HR, cardiac contractility, and vascular resistance via increased sympathetic outflow. Conversely, a rise in BP (more stretch) elicits reflex sympathetic inhibition and parasympathetic activation causing a decrease in HR, cardiac contractility, and vascular resistance (Lanfranchi & Somers, 2002). The baroreceptors signal changes in arterial pressure over a wide range, from approximately 50-150mmHg (Dampney et al., 2002).

Another negative feedback system responsible for regulating BP is the chemoreflex. The chemoreceptors are located in the carotid sinus and the aortic arch in small structures called carotid bodies and aortic bodies respectively (Tortora & Garbowski, 1996). These receptors are sensitive to a lack of oxygen or an excess of carbon dioxide or hydrogen ions. Whenever arterial pressure falls below a certain level, the chemoreceptors become stimulated because of reduced blood flow to the carotid or aortic bodies and hence a diminished availability of oxygen and a build up of carbon dioxide and hydrogen ions. This stimulation of the carotid or aortic bodies is then transmitted to the cardiovascular center that reflexly evokes an increase in sympathetically mediated vasoconstriction in most blood vessels as well as an increase in ventilation (Dampney et al., 2002). Chemoreceptors are not a very powerful regulator of BP as they are not strongly stimulated until DBP falls below 80mmHg (Guyton et al., 1996).

In addition to input from the peripheral receptors, the cardiovascular center also receives input from higher brain regions. The cardiovascular and respiratory changes that occur at the onset of exercise, including increased HR and ventilatory rate are thought to be a result of "central command" (Dampney et al., 2002).

2.1.2 Hormonal Regulation

Hormonal control of the circulation refers to the secretion or absorption of substances into the body. Some of these substances, or hormones, are formed in specialized glands and act systemically in the body while others are produced in local tissues and have a local effect (Guyton et al., 1996).

One of the most potent vasoconstrictor substances is norepinephrine. Produced in the adrenal medulla, this hormone increases HR and cardiac contractility in addition to causing vasoconstriction of blood vessels. When the sympathetic nervous system is activated, nerve endings in the individual tissues also release norepinephrine. When the adrenal medulla itself is sympathetically activated, norepinephrine is circulated in the blood and has the same excitatory effect as direct sympathetic input (Guyton et al., 1996).

The renin-angiotensin-aldosterone (RAA) system plays a key role in arterial BP regulation. When blood volume falls or blood flow to the kidney's decreases, the kidneys release an enzyme called renin into the blood stream. Renin acts to form angiotensin I which, as it passes through the lungs, is converted to angiotensin II by angiotensin converting enxyme (ACE). Angiotensin II causes vasoconstriction which in turn increases total vascular resistance. Also, angiotensin II stimulates the secretion of aldosterone which increases sodium and water reabsorption by the kidneys and therefore

increasing total blood volume and BP (Abboud, 1982). Other factors that contribute to the regulation of BP include endothelin, vasopressin, and prostaglandins, and nitric oxide (Guyton et al., 1996).

2.2 Hypertension

2.2.1 Introduction

CVD is responsible for 16.7 million deaths every year worldwide and is emerging as a major contributor to the global disease burden (WHO, 2003). The development and progression of CVD is preceded by numerous risk factors. While some risk factors can not be changed, including age, gender, and family history, others are modifiable. Modifiable risk factors include dyslipidemia, diabetes mellitus, hypertension, obesity, tobacco use, and physical inactivity (CACR, 1999).

Due to increasing longevity and increased prevalence of unhealthy lifestyles, hypertension is becoming a common health problem. Hypertension is estimated to afflict 1 billion individuals worldwide and cause 7.1 million global deaths each year (Chobanian et al., 2003). More specifically, hypertension plays a key etiologic role in the development of ischemic or coronary heart disease, cerebrovascular disease, cardiac and renal failure (2003; Kannel, 1996).

According to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003) hypertension is defined as SBP of 140 mmHg or greater, and/or DBP of 90mmHg or greater, or taking antihypertensive medication. A positive relationship between BP and CVD outcomes

exists that is "strong, independent, predictive, and etiologically significant" (Chobanian et al., 2003).

More recently, the BP designation of "prehypertension" (SBP 120-139mmHg and/or DBP 80-89mmHg) has been introduced in the literature (Chobanian et al., 2003). This new classification is intended to identify people who may benefit from lifestyle modifications in an attempt to prevent future development of hypertension.

To underscore the potential CVD risk associated with "prehypertension", a follow-up study of participants in the Framingham Heart Study was conducted (Vasan et al., 2001). It was found that men and women with "prehypertension" BP levels at baseline examination had a higher incidence of CVD on follow-up compared to those with optimal BP. These results suggest that perhaps even those with "prehypertension" may benefit from BP lowering therapy to prevent future disease.

Although the standard definition of hypertension includes an elevation of SBP and/or DBP, increased pulse pressure (PP) is now being recognized a predictor of CVD risk and mortality (Benetos, Rudnichi, Safar, & Guize, 1998). PP, the difference between SBP and DBP, is considered the pulsatile component of blood pressure (Guyton et al., 1996). The major determinants of PP are stroke volume output of the heart and the visoelastic properties of large arteries (Guyton et al., 1996). Increased PP is a function of an isolated increase in SBP and a consistent or decreasing DBP. This phenomenon has been attributed to a progressive stiffening of the arterial tree with age (Franklin et al., 1997).

Several studies have examined the efficacy of using PP measures to predict CVD risk and mortality. One examination in the French male population showed that a wide PP (<45mmHg to ≥65mmHg) was an independent and significant predictor of all-cause, total cardiovascular, and coronary mortality (Benetos et al., 1997b). These findings were consistent across both young (<55y) and older (≥55y) subjects with relatively low CVD risk. Gasowski et al. (2002) defined the relationship between increased PP and mortality more simply. They noted that in individuals with hypertension, a 10mmHg wider pulse pressure at baseline was independently associated with 6-7% increases in risk of both all cause and CVD mortality (Gasowski et al., 2002). It is important to consider whether the association between PP and CVD risk noted in the above studies is causal or whether it represents underlying vascular disease, which may lead to CVD.

2.2.2 Pathophysiology

Approximately 90-95% of individuals with hypertension have what is termed "essential hypertension". This term means that the hypertension has no known origin. The pathological mechanisms in hypertension may involve the RAA system, the sympathetic nervous system, the secretion of nitric oxide and other vasoactive substances (Rao, 2003) as well as age associated arterial stiffening (Rowe, 1987).

The importance of the RAA system in long term BP regulation is firmly established (Rao, 2003). A crucial feature of this system is the ability of the kidneys to respond to changes in arterial pressure by altering renal excretion of salt and water (pressure natriurisis). As arterial pressure or sodium intake increases, the RAA system is

suppressed, which enhances the ability of the kidneys to excrete water and salt. This mechanism is defective in some individuals with hypertension (Lohmeier, 2001).

Hyperactivity of the sympathetic nervous system is a hallmark observation in essential hypertension (Abboud, 1982). Increased sympathetic nerve activity has the potential to contribute to hypertension in various ways. Sympathetic neural drive to the kidney causes sodium and water retention as well as activation of the RAA system. These result in an increased vascular resistance and increased blood volume. Also, sympathetic excitation in the blood vessels may cause sustained vasoconstriction while sympathetic drive to the heart increases HR and stroke volume (Abboud, 1982).

The endothelium constitutes the monolayer of cells that line the inner surface of blood vessel walls. Previously thought to be inert, it is now recognized that the endothelium secretes a number of vasoactive substances including nitric oxide (NO). NO, the most important vasodilator secreted by a healthy endothelium, is responsible for maintaining normal BP. However, endothelial dysfunction is characterized by a defect in the release or synthesis of NO (Sherman, 2000). This may be one of the mechanisms that contribute to the pathogenesis of essential hypertension.

Finally, advancing age is associated with a progressive reduction in the vascular distensibility of major vessels (Benetos, Laurent, Asmar, & Lacolley, 1997a). The clinical consequences of this arterial stiffening are increased SBP and decreased carotid arterial baroreflex sensitivity (Rowe, 1987). This phenomenon contributes to essential hypertension and the development of isolated systolic hypertension.

2.2.3 Treatment

The goal of hypertension management is to reduce morbidity and mortality by the least intrusive means possible. This may be accomplished by reducing and maintaining SBP below 140mmHg and DBP below 90mmHg while controlling other modifiable CVD risk factors. Treatment to even lower levels may be useful for the prevention of stroke, heart failure, and renal failure (Chobanian et al., 2003). These BP targets may be attained through lifestyle modifications, alone or in combination with pharmacological therapy.

Anti-hypertensive drug therapy has been associated with a reduction in stroke incidence (30-35%), myocardial infarction (20-25%), and heart failure (>50%) (Neal, MacMahon, & Chapman, 2000). Four major classes of anti-hypertensive agents exist including diuretics, beta-blockers, calcium-channel blockers, and ACE inhibitors. With regard to total cardiovascular mortality, there does not appear to be convincing differences between outcomes as a result of treatment with the different drug classes. However, depending on the individual and the outcome being measured, certain drug classes may prove more efficacious (Chobanian et al., 2003).

Diuretics act to reduce the reabsorption of water and salt by blocking the active transport of sodium through the tubular wall of the kidney. This promotes diuresis and consequently, BP is reduced due to decreased blood volume. Beta-blockers, calcium-channel blockers, and ACE inhibitors can be classified as vasodilator agents. Beta-blockers inhibit sympathetic nervous signals to cause decreased HR and cardiac contractility as well as decreased peripheral vascular resistance. Calcium-channel blockers inhibit the entry of calcium into vascular smooth muscle cells resulting in

peripheral and coronary arterial vasodilation. Recalling that angiotensin II is a potent vasoconstrictor, ACE inhibitors operate by blocking the conversion of angiotensin I to angiotensin II and thereby reducing vasoconstriction (ACSM, 2000).

Although these medications, either alone or in combination, have been proven to reduce BP to target levels, they are not without limitations. A variety of side effects accompany most of these drugs, some which may have serious implications for the patient's quality of life (Ciccone, 1996). Also, both the personal and public costs associated with these medications cannot be overlooked. Most importantly, only 30% of individuals receiving pharmacologic treatment for hypertension are treated to appropriate targets (CACR, 1999). The startling fact that 70% of diagnosed individuals do not obtain sufficient BP reductions with pharmacologic treatment indicates that other treatment avenues need to be explored.

Adoption of healthy lifestyles by all people is critical for the prevention and management of hypertension. Numerous modifiable risk factors, including obesity, physical inactivity, high dietary salt intake, stress, and high alcohol consumption, are associated with the development and progression of hypertension (WHO, 2003). Therefore, if these factors can be targeted by treatment strategies high BP is eminently preventable.

Suggested dietary modifications include the adoption of a diet that is rich in fruits, vegetables, and low fat dairy products with a reduced content of cholesterol and saturated fats. Dietary sodium should be no more than 2.4 g per day. Alcohol consumption should be limited to two drinks per day for men and one drink per day for

women (Chobanian et al., 2003). Finally, it is recommended that every adult should accumulate 30 minutes or more of moderate intensity physical activity on most, preferably all, days of the week to prevent and manage high BP (Pescatello et al., 2004).

In contrast to pharmacological therapy, lifestyle modifications are typically not accompanied by adverse side effects. To the contrary, quality of life may be improved by the adoption of a healthier lifestyle that includes dietary and activity based changes. However, is well recognized that exercise and diet control are complex behavioural patterns (Kaplan, Sallis, & Patterson, 1993). Therefore, adoption of and adherence to such regimens is always an issue.

2.3 Exercise and Blood Pressure Regulation

Physical activity is inversely associated with morbidity and mortality from CVD (Blair et al., 1989) and has been shown to have a beneficial effect on BP (Whelton et al., 2002). A number of studies have retrospectively examined the association between lifetime physical activity and the incidence of hypertension. Paffenbarger et al. (1983) reported that male university alumni who engaged in vigorous exercise during and after university were less likely to develop hypertension when compared to their sedentary peers (Paffenbarger, Jr., Wing, Hyde, & Jung, 1983). Also, results from a 10 year follow-up study suggest that the total amount and intensity of leisure time physical activity were inversely related to the development of hypertension in middle aged men (Haapanen, Miilunpalo, Vuori, Oja, & Pasanen, 1997). Both the acute and chronic effects of various forms of exercise will be examined regarding their impact on BP.

2.3.1 Aerobic Exercise – Acute Regulation

During dynamic exercise, cardiac output increases significantly to ensure adequate perfusion of the exercising musculature. This increase is achieved by a withdrawal of parasympathetic tone, an increase in sympathetic activity, and pronounced vasoconstriction in the venous vasculature. In parallel, the need for increased blood flow and oxygen delivery to the exercising muscle is achieved by regional vasodilatation of the arterioles perfusing the exercising tissue in combination with a vasoconstriction of arterioles supplying the non-active tissue (MacDonald, 2002). Increased cardiac output and vasoconstriction to the non-exercising vascular beds increases SBP. However, the significant vasodilation at the exercising vascular beds helps to buffer this increase and results in only a minimal rise in DBP (MacDonald, 2002).

Following a bout of aerobic activity there appears to be an immediate and sustained decrease in arterial blood pressure. This phenomenon is termed post exercise hypotension (PEH) and can persist for up to 22 hours after exercise (Pescatello, Fargo, Leach, Jr., & Scherzer, 1991; Pescatello et al., 2004). Although PEH occurs in normotensive individuals, reductions in SBP and DBP as great as 15 and 4mmHg respectively have been noted in hypertenisve subjects (Pescatello & Kulikowich, 2001). These acute decreases in BP are clinically significant and offer hypertenisive individuals the benefit of having their BP transiently lowered (Pescatello et al., 2004). A definitive mechanism underlying PEH is not known at this time. The decreased BP following exercise is mainly attributed to decreased vascular resistance. The underlying cause for this reduced vascular resistance had not yet been determined (MacDonald, 2002).

2.3.2 Aerobic Exercise – Chronic Regulation

An abundance of interventional studies exist regarding the effect of aerobic exercise training on BP. A comprehensive meta-analysis based on randomized, controlled clinical trials examined this relationship (Whelton et al., 2002). The 54 trials analysed were conducted between 1986 and 2000 and varied in size from 8 to 247 participants. All trials were conducted in adults (>21 years) and the exercise interventions varied in length from 3 weeks to 2 years. Important variables such as BP at baseline and body mass index were considered. Results indicated that aerobic exercise was associated with a significant reduction in both SBP (3.84 mmHg) and DBP (2.58 mmHg). This reduction in BP was seen in hypertensive as well as normotensive subjects and in both overweight and normal weight participants. Also, BP reduction was not significantly related to change in body weight. This is an indication that the effects of aerobic exercise on BP may be independent of weight loss.

A considerably smaller meta-analysis of seven randomized controlled trials examined the impact of aerobic exercise on BP in older adults (>50 years) (Kelley & Sharpe, 2001). The results of this meta-analysis indicated that aerobic exercise resulted in a significant reduction in SBP by 2% and a non-significant decrease in DBP by 1%. This finding of reduced SBP is of particular importance when considering that many older adults are afflicted with isolated systolic hypertension (Franklin et al., 1997). Although progressive stiffening of the arterial tree often underlies increases in SBP, the results of these two meta-analyses suggest that aerobic exercise has the potential to beneficially modify this outcome.

Due to the complex nature of BP regulation, the precise mechanism underlying the BP reductions following aerobic exercise is not known. MAP is a function of cardiac output and total peripheral resistance. Cardiac output is not significantly reduced following training; thus decrease total peripheral resistance seems to be the primary mechanism for BP reductions following training. Decreases in vascular resistance after training are mediated by structural and neurohumoral adaptations, altered vascular responsiveness to vasoactive substances, or both. Larger lumen diameter and greater arterial distensibility of the blood vessels are structural adaptations to training that will lower total vascular resistance. A reduction in sympathetic neural influences or a greater local vasodilator influence (e.g. nitric oxide) would reduce the vasoconstrictor state of the vasculature and result in decreased resistance (Pescatello et al., 2004).

2.3.3 Resistance Exercise – Acute Regulation

Although many health organizations advocate aerobic exercise as a means to prevent and manage hypertension (2003; Chobanian et al., 2003), there is often little mention of resistance exercise as a potential therapy. Resistance exercise elicits pronounced increases in SBP and DBP. This increase in BP is due to sympathetic vasoconstriction in non-exercising vascular beds and mechanical compression of the blood vessels in the exercising muscle beds (MacDonald, 2002). Unlike the PEH that occurs with aerobic exercise, BP is not significantly lower following an acute bout of resistance exercise in a 24 hour follow up period (Roltsch, Mendez, Wilund, & Hagberg, 2001).

For many years resistance exercise training was contraindicated for individuals with hypertension or heart disease (McCartney, 1998). Early studies on healthy young individuals measured SBP values in excess of 400mmHg during heavy weight lifting (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985). It was felt that this type of exercise would place an unnecessary pressure stress on an already compromised cardiovascular system. More recently however, studies have examined the BP response to more practical lifting intensities (McCartney, 1998). It has been concluded that resistance training is a safe and effective mode of exercise for the majority of the population, including individuals with heart disease.

2.3.4 Resistance Exercise – Chronic Regulation

Studies that have examined the chronic effects of resistance training on BP have produced conflicting findings. In a study involving sedentary men, evidence exists that a 16 week whole body resistance training program did not result in a reduction of SBP or DBP (Van Hoof et al., 1996). Conversely, a number of studies have found that resting BP can be reduced by resistance training (Harris & Holly, 1987; Hurley et al., 1988). Harris and Holly (1987) reported that 9 weeks of circuit weight training slightly improved DBP (from 95.8 to 91.3 mmHg) in borderline hypertensive subjects.

A meta-analytic approach was adopted to examine the effects of progressive resistance training on resting SBP and DBP. Kelley and Kelley compiled data from 11 randomized controlled studies which corresponded to the assessment of 320 participants. Chosen studies ranged from 6 to 30 weeks in length with an exercise frequency of 2 to 5 times per week. Subjects exercised at an intensity that ranged from 30-90% 1RM.

Results indicated that across all studies, decreases of approximately 2% (3mmHg) and 4% (3mmHg) were found in resting SBP and DBP respectively.

Interestingly, only 20% of the studies reviewed by Kelley and Kelley included subjects whose initial BP was greater than 140/90mmHg. This may be an explanation of why such a small BP lowering effect was noted (Kelley & Kelley, 2000). Future studies need to examine hypertensive subjects as they have the most to gain from lowering their resting BP. Also, an optimal training protocol needs to be identified before resistance training is commonly prescribed as a lifestyle modification that will improve BP.

The mechanisms by which resistance training may influence BP are not clear. Strength training can acutely elevate BP and in general does not improve $VO_{2max.}$ It is possible that modest repeated rises in SBP and DBP during the training session serve as the stimulus for a decrease in resting BP (Van Hoof et al., 1996).

2.3.5 Isometric Exercise – Acute Regulation

Isometric contractions elicit marked increases in both SBP and DBP, while HR is increased only slightly. When fatiguing isometric contraction are performed with a larger muscle mass (i.e. quadriceps muscle versus finger flexor muscle) both HR and BP increase to a greater extent (Smolander et al., 1998). Also, lower intensity isometric contractions (i.e. 20% of a maximal voluntary contraction (MVC) versus 40% MVC) produced a less exaggerated HR and BP response. Currently no studies are available to describe the post exercise BP response to isometric exercise.

2.3.6 Isometric Exercise – Chronic Regulation

The hypotensive effects of isometric exercise training are currently under investigation. Kiveloff and Huber offered the first evidence in this area 30 years ago (Kiveloff & Huber, 1971). Participants were to follow a 5-8 week program of whole body isometric exercise that was performed 3 times per day for 5 days. Significant reductions in BP were noted in hypertensive participants ranging from 6-42 mmHg in SBP and 2-24 mmHg in DBP. Five subjects who were receiving a constant dosage of anti-hypertensive drugs also showed reductions in BP ranging from 4-28 mmHg for SBP and from 2-14 mmHg for DBP (Kiveloff et al., 1971). Because the exercise regime was difficult to quantify and due to the fact that no control group data was reported strong conclusions about the potential beneficial effects of isometric exercise training could not be drawn from this study. In 1985, a purely observational study reported that the incidence of hypertension was lower in occupations classified as having a moderate or high isometric activity component as compared to those classified as low (Buck & Donner, 1985).

To make any conclusive statement regarding the efficacy of isometric training as a therapy to reduce BP, randomized controlled trials are necessary. Wiley et al. (1992) was the first to assess the effect of isometric training on resting BP with a controlled experiment. The isometric exercise used in this study consisted of brief handgrip contractions separated by rest periods. Participants were selected for having high-normal DBP and trained with four 2-minute contractions separated by three minutes of rest. Training intensity was 30% of their maximum handgrip effort for each day. The IHG was performed three times per week for 8 weeks. Measurements of resting BP were taken

in the seated position prior to each training session following 10 minutes of seated rest. Results indicated that, when compared to the control group, the isometrically trained group demonstrated a reduction in SBP (from 134.1 to 121.4 mmHg) and DBP (from 86.5 to 71.6 mmHg) over the 8 weeks (Wiley et al., 1992).

In a second study, using a similar protocol of brief isometric contractions followed by rest periods, Wiley et al. (1992) noted that after five weeks of IHG training, SBP decreased from127 to 117.5mmHg and DBP was reduced from 86.2 to 77.4 mmHg. Following a 5 week period of de-training both SBP and DBP returned to baseline values in these subjects. It should be noted that these results were obtained in the absence of a non-exercising control group (Wiley et al., 1992).

These results strongly implicate isometric training as a potential therapy to reduce resting BP. Interestingly, these remarkable reductions in BP were noted with only small increases in BP during the handgrip. SBP taken in the final 30 seconds of the first 2-minute handgrip contraction revealed an increase of 16.8mmHg while DBP increased by 15.9mmHg (Wiley et al., 1992). Therefore, brief, interrupted isometric efforts are highly effective and time efficient while avoiding the higher BP values associated with fatiguing contractions.

More recently, studies have attempted to repeat these impressive findings and pinpoint a mechanism responsible. Ray et al. attempted to determine whether IHG exercise lowers resting BP and whether potential reductions may be due to reduction in efferent muscle sympathetic nerve activity (MSNA) (Ray et al., 2000). Young healthy, normotensive subjects were assigned to a training, sham-training, or control group. The

training protocol consisted of four 3-minute bouts of IHG exercise at 30% MVC separated by 5-minute rest periods. Following 5 weeks of 4 times per week training, DBP decreased significantly (from 67 to 62mmHg) as did MAP (from 86 to 82mmHg) with no change in the control or sham groups. However, neither SBP nor MSNA changed significantly following training. Although providing more support for the efficacy of isometric exercise, this study was unable to determine a mechanism responsible for the observed reductions in BP.

Previous accounts of BP reduction following IHG exercise have involved young subjects with either normal or high-normal BP (Ray et al., 2000; Wiley et al., 1992). Taylor et al. (2003) examined the impact of IHG on resting BP, HR variability, and BP variability in older individuals with hypertension in a controlled trial. HR variability and BP variability were used as non-invasive indicators of sympathovagal balance. Alterations in autonomic regulatory balance may exacerbate hypertension or underlie a therapy that reduces BP. Nine subjects performed four 2-minute IHG contractions at 30% MVC, 3 days per week for 10 weeks. Eight subjects acted as non-exercising controls. Interestingly, most of the individuals in this study were already using anti-hypertensive medications. After training, significant reductions were noted in SBP (from 156mmHg to137 mmHg) as well as in MAP (from 107mmHg to 96 mmHg). Also, the low frequency to high frequency ratio for HR and BP variability decreased indicating a decreased sympathetic, and an enhanced parasympathetic modulation of both HR and BP (Taylor et al., 2003).

Several other investigations have noticed a reduction in sympathetic outflow following forearm exercise (Sinoway et al., 1996; Somers et al., 1992; Mostoufi-Moab, Widmaier, Cornett, Gray, & Sinoway, 1998). Other proposed mechanisms responsible for the hypotensive effect of isometric exercise include enhanced baroreflex control of sympathetic outflow (Somers, Conway, Johnston, & Sleight, 1991; Silva, Brum, Negrao, & Krieger, 1997), and improved endothelial function (DeSouza et al., 2000; Higashi et al., 1999b; Higashi et al., 1999a; Sun, Huang, Koller, & Kaley, 1998) . Also, an increase in arterial distensibility has been proposed (Tanaka et al., 2000; Cameron et al., 1994; Vaitkevicius et al., 1993; Kingwell, Berry, Cameron, Jennings, & Dart, 1997). Improved arterial distensibility may improve baroreflex sensitivity and hence alter SNS outflow.

Compelling evidence supports isometric exercise and IHG in particular, as an effective means of lowering resting BP. Although some accounts outline mechanisms that may be responsible for the reduction in BP, there is no consensus in the literature. Therefore, the goal of future studies in this area should be twofold; first, to identify the training protocol that will lower BP most effectively, and second, to identify the mechanism, or mechanisms, that underlie this reduction.

2.4 Arterial Distensibility

2.4.1 Arterial Physiology

Structural and/or functional alterations in the arterial system may underlie BP changes observed with IHG exercise. The arterial system has two distinct yet interrelated functions: first to deliver an adequate supply of blood to different tissues and second, to transform the pulsatile ejection of blood from the left ventricle to a smooth and continuous peripheral flow (Izzo, Jr. & Shykoff, 2001). Structurally, arteries are composed of three layers. The inner layer, the tunica intima, is composed of a lining of endothelium that is in contact with the blood, a basement membrane, and a layer of elastic tissue called the internal elastic lamina. The middle layer, the tunica media, is the thickest and consists of elastic fibers and smooth muscle fibers. Finally, the outer layer, or the tunica adventitia is composed of mainly of elastic and collagen fibers (Faury, 2001).

Arterial distensibilty is a measure of an artery's ability to expand and contract with cardiac pulsation and relaxation. Arteries principally function as "cushions" whereby they dampen the pressure oscillations resulting from intermittent ventricular ejection via their distensible nature (Safar et al., 1987). This feature allows for continuous perfusion of organs and tissues. During systole, the aorta expands to accommodate the stroke volume and recoils during diastole to promote forward flow (Somers et al., 1992; Edwards & Diana, 1978). Pressure increases during systole (SBP) due to the limited capacity of the aorta and this pressure is partially maintained during diastole (DBP) by the rebounding of the expanded arterial wall. Therefore when the arteries become less

distensible, this cushioning function is impaired resulting in higher SBP and lower DBP (Arnett et al., 1994).

It is generally accepted that, in terms of vascular mechanics, the composition of blood vessels influences the distensibility of the vessel wall. This concept describes the relationship between the structure and the function of the vessel wall in terms of vascular smooth muscle, collagen, and elastic properties (Benetos et al., 1997a). Elastic properties of a vessel allow it to be stretched under a pressure load while retaining its ability to return to its original shape when the pressure is removed. Collagen fibers allow for arterial expansion over a physiologic range of pressure but protect the artery from yield or rupture. Differences in the ratio of elastin to collagen affect distensibility. The lower the ratio of elastin to collagen, the stiffer the artery is. Elevations in smooth muscle tone and or smooth muscle cell hypertrophy also increases stiffness (Arnett et al., 1994).

Reduced arterial distensibility contributes to a disproportionate increase in SBP and PP (Arcaro, Laurent, Jondeau, Hoeks, & Safar, 1991; Van Merode, Hick, Hoeks, Rahn, & Reneman, 1988; Armentano et al., 1995; Benetos et al., 1997a). This increase in PP has been associated with cardiovascular morbidity and mortality (Benetos et al., 1997b; Gasowski et al., 2002). In addition to its undesirable impact on BP, reduced arterial distensibility is now recognized as an independent risk factor for CVD (Arnett et al., 1994).

2.4.2 Consequences of Reduced Arterial Distensibility

Numerous adverse cardiovascular effects accompany the reduction in the distensibilty of arteries in the central circulation.

Firstly, the ejection of the stroke volume into a non-compliant aorta can result in an elevation of SBP, while the accompanying loss of elastic recoil causes a reduction in DBP. Therefore, arterial PP has effectively been increased. If SBP and the PP are elevated chronically, vascular damage may occur and/or atherosclerosis will be exacerbated (Seals, 2003). Consequently, the risk of myocardial infarction, thrombosis, and stroke are increased.

Secondly, both cardiac function and structure may be affected by reduced large artery compliance. This includes left ventricular hypertrophy, increased LV oxygen demand, prolonged myocardial contraction, and reduced early diastolic filling rate (Seals, 2003). The consequences of the above alterations include an increased risk of congestive heart failure for the elderly individual.

Finally, decreased compliance of large central arteries can reduce the responsiveness of essential reflexes involved in maintaining circulatory homeostasis (Hunt et al., 2001). In response to a stiff aorta and carotid sinus, there is less deformation of the arterial wall in response to increased intravascular pressure. This results in a decreased afferent signalling by the arterial barorecptors to the central nervous system. Consequently, there is a smaller efferent response which contributes to decreased BP variability and possibly a reduced resistance to ventricular fibrillation and a susceptibility to sudden cardiac death (Hunt et al., 2001).

2.4.3 Measurement

Many methodologies, both invasive and non-invasive have been applied to the assessment of arterial distensibility *in vivo*. Two popular non-invasive assessment techniques include pulse wave velocity (PWV) and ultrasound imaging.

PWV is an indirect measure of arterial distensibility and has been shown to increase with aging and hypertension. The velocity of travel of a pressure waveform along an artery is inversely related to the distensibility of the arterial segment between measurement sites (Izzo, Jr. et al., 2001). Pressure waveforms are captured by transducers placed over the artery and velocity is determined by dividing the distance travelled between the transducers (meters) by the time of travel of the pulse wave (the propagation time in seconds). Propagation time is the elapsed time between the detection of the peripheral pulse at two different transducers and is determined by estimating the delay between two consecutive waveforms (Arnett et al., 1994).

This technique however is not without its limitations. Measurement error can be substantial, including problems related to the measurement of both transit time and distance travelled by the pulse wave. Timing is mainly affected by difficulties in identification of the predetermined part of the pulse wave that will be measured at both points. Also, individual differences in vascular anatomy can lead to inaccuracies in determining the actual distance between the measurement sites (Izzo, Jr. et al., 2001).

Direct measurement of distensibility requires the simultaneous measurement of arterial diameter or cross sectional area and the associated pressure. More specifically, the diameter change in one heart cycle and the associated PP are measured. Ultrasound is

the most frequently used imaging modality and allows for the visualization of the vessel diameter (Izzo, Jr. et al., 2001). The ultrasound transducer is placed to direct ultrasound beams perpendicular to the artery to obtain the best possible sound reflection from the arterial wall (Arnett et al., 1994).

Simultaneously to the diameter measurement, a corresponding pressure measurement is obtained. In the past, BP measured at the brachial artery was used in the distensibility calculations. However, because PP tends to become amplified in the periphery, these pressure measurements may not represent central artery pulse pressure (Oliver & Webb, 2003). Therefore, applanation tonometry is now used to obtain PP measures in the artery of interest. The principle of applanation tonometry assumes that if one can flatten, or applanate, the curved surface of a pressure containing structure, then the circumferential stresses in the wall of the structure are balanced and the pressure obtained by the sensor is the same as intra-arterial pressure (Kelly, Hayward, Avolio, & O'Rourke, 1989; Oliver et al., 2003). This technique is not normally used to measure absolute pressure. However, brachial artery MAP and DBP can be assumed to be equal to that in the artery of interest so that the absolute pressure of the artery of interest can be calculated (Oliver et al., 2003).

Advantages of standard ultrasound techniques are their impressive technical precision and test reproducibility. However, measurement error can arise from a number of sources. The pressure from the transducer over the artery may distort the vessel and potentially underestimate vessel diameter change. Also, the acquisition of accurate data may be restricted by participant effects including respiratory movements or persistent

swallowing. Finally, incorrect identification of the arterial walls during analysis may produce inaccurate results (Arnett et al., 1994).

2.4.4 Effect of Aging

Age is considered the main clinical determinant of large artery stiffness. The distensibility of the large arteries in the central circulation decreases markedly with increasing age in adult humans (Rowe, 1987; McVeigh et al., 1999). A 40% to 50% decrease in carotid artery distensibility, which translates to a 20-25mmHg elevation in SBP, has been observed in healthy, sedentary men and women from the ages of 25 to 75 years (Tanaka et al., 2000). As noted previously, this stiffening of the aorta and other large arteries observed with increasing age places elderly individuals at risk for cardiovascular morbidity and mortality (Seals, 2003).

Although the underlying basis for these age dependant changes is not completely understood, it is believed that structural changes play a major role. These changes include increased fraying and fragmentation of elastin, a progressive deposition of calcium salts, and an increase in the number and cross linking of collagen fibers (McVeigh et al., 1999; Benetos et al., 2002). These alterations are essentially due to tissue fatigue (Benetos et al., 1997a). Interestingly, this age associated stiffening appears to only affect central, elastic arteries. The distensibility of muscular arteries does not seem to decrease with age (Izzo, Jr. et al., 2001).

2.4.5 Hypertension

In addition to aging, hypertension also has an undesirable impact on arterial distensibility. Increased mechanical stress on the arteries is proposed as the stimulus for

changes in distensibility with hypertension (Benetos et al., 1997a). The major structural alteration of the vessel wall associated with hypertension is hypertrophy of the muscular layer (Benetos et al., 2002). Other structural modifications in the arterial wall in response to hypertension include changes in the extracellular matrix, specifically an accumulation of collagen (Safar et al., 1987). It is important to note the bi-directionality of the relationship between hypertension and distensibility. Although hypertension has the ability to decrease arterial distensibility, the stiffness of an artery also has a direct impact on both SBP as well as PP (Dart & Kingwell, 2001). Interestingly, despite the development of arterial hypertrophy, distensibility of the peripheral, muscular arteries does not seem to be modified (Izzo, Jr. et al., 2001). Central, elastic arteries however, experience decreased distensibility (Benetos et al., 1997a).

2.5 Exercise and Arterial Distensibility

Regular aerobic exercise has been shown to improve BP (Whelton et al., 2002) as well as decrease CVD morbidity and mortality (Blair et al., 1989). The impact of resistance training on BP and CVD risk remains equivocal however (Kelley et al., 2000). Is has been proposed that improved arterial distensibility may be one of the mechanisms responsible for the beneficial adaptations seen with aerobic training. The impact of both aerobic and resistance exercise on arterial distensibility have been investigated.

2.5.1 Aerobic Exercise

Support for the role of regular aerobic exercise in the primary prevention of decreases in arterial distensibility is currently based mainly on results from cross

sectional studies (Vaitkevicius et al., 1993) (Tanaka et al., 1998). In conjunction with the Baltimore Longitudinal Study of Aging, Vaitkevicus and colleagues (Vaitkevicius et al., 1993) examined central artery distensibility in men and women between the ages of 21 to 96 in addition to assessing their aerobic capacity as indexed by their maximal oxygen uptake (VO_{2max}). It was found that older males with higher physical conditioning status demonstrated reduced central arterial stiffness when compared to their older sedentary peers. Similar results have been noted in females where age related increases in central arterial distensibility were not observed in post menopausal endurance trained women versus their sedentary counterparts (Tanaka et al., 1998).

Previous research indicates that regular, vigorous endurance training holds the greatest potential to attenuate age associated arterial stiffening (Tanaka et al., 1998; Tanaka et al., 2000; Vaitkevicius et al., 1993). Recreational and leisure time physical activity also have been shown to slow the progression of arterial stiffening yet to a smaller extent (Schmidt-Trucksass et al., 1999; Tanaka et al., 2000). Using a self administered questionnaire, the association of self selected leisure time physical activity and common carotid distensibility was assessed (Schmidt-Trucksass et al., 1999). Results indicated that in males between 16 to 78 years, a higher level of leisure time physical activity was associated with significantly increased arterial distensibility. Tanaka et al. (2000) compared carotid artery distensibility in individuals who were sedentary, recreationally active, or endurance trained (Tanaka et al., 2000). It was found that arterial distensibility in the endurance trained group was 20 to 35% higher than in the two less active groups. It should also be noted that arterial distensibility in the recreationally

active group was 10 to 17 % higher versus the sedentary group. This finding however was not statistically significant. Therefore is seems that vigorous aerobic exercise may be the most effective at modifying central arterial compliance. Recreational activity may have a small, but physiologically important, effect on arterial distensibility. It is important to recall that the studies by Schmidt-Trucksass (1999) and Tanaka (2000) involving leisure time physical activity are cross-sectional in nature. Therefore, the differences observed between trained and sedentary groups can not be attributed solely to the effects of regular exercise. Other factors including lifestyle and genetic influences need to be considered.

These cross sectional findings form an excellent foundation for recommendations regarding methods of preventing or attenuating the age associated decline in distensibility. However, to determine the potential efficacy of regular aerobic exercise for restoring the loss of arterial distensibility with aging, an interventional approach is required.

Evidence regarding the ability of aerobic exercise to reverse the age associated decline in central arterial compliance is equivocal. Total systemic arterial compliance was improved in sedentary, young, healthy males following a 4 week cycling program (Cameron et al., 1994). Interestingly, it was also noted that the increase in systemic arterial compliance was greater than that due to changes in BP and is likely to include a component due to change in intrinsic arterial compliance. Although these results are promising, the subjects involved were young, healthy individuals who most likely have

not experienced age associated arterial stiffening and do not require interventions that will improve it.

Tanaka et al. (2000) examined the impact of a three month aerobic exercise intervention (primarily walking), on the arterial distensibility of 20 middle aged and older men with normal BP. Independent of alterations in body mass, BP and VO_{2max}, central arterial distensibility increased in response to the training stimulus (Tanaka et al., 2000). These results provide the first longitudinal experimental evidence that regular aerobic exercise can partially reverse the reduction in large artery distensibility that accompanies aging. With regards to practicality, it is important to note that these positive alterations in arterial distensibility were achieved with brisk walking, a mode and intensity of exercise that the most individual could partake in.

Exercise interventions involving individuals with isolated systolic hypertension did not, however, result in positive changes in arterial distensibility (Ferrier et al., 2001). Following 8 weeks of moderate intensity cycling, no improvements in systemic arterial compliance were found in the exercise versus the sedentary control group. This data suggests that perhaps the large artery stiffness associated with isolated systolic hypertension is resistant to modification through aerobic training. It is important to note that the duration of the study was quite short. Perhaps a more intensive or longer duration intervention is required to improve distenisbility in this clinical population.

Although aerobic exercise has been proven to improve central arterial ditensibility (Cameron et al., 1994; Schmidt-Trucksass et al., 1999; Tanaka et al., 1998; Tanaka et al., 2000; Vaitkevicius et al., 1993) no studies have examined the impact of aerobic exercise

on peripheral artery distensibility. Following a study of pre and post menopausal women, there was no age associated decrease in distensibility observed in peripheral arteries. Therefore, peripheral arteries may not benefit from aerobic training as their function does not deteriorate with aging.

The mechanisms through which regular aerobic exercise can alter arterial distensibility are complex and have not received extensive study. However, it was noted that collagen cross linking in the left ventricle of endurance trained rats was less than 50% of that observed in sedentary controls (Thomas, Zimmerman, Hansen, Martin, & McCormick, 2000). Although no definitive mechanisms have been identified, it can be assumed that any influence of aerobic exercise should involve an attenuation or reversal of one or more of the mechanisms that have been proposed to contribute to the age associated decline in compliance.

2.5.2 Resistance Exercise

While aerobic exercise prevents and perhaps reverses age associated arterial stiffening, the impact of resistance training has not been extensively studied. Employing a cross sectional design, Bertovic et al. (1999) were the first to compare arterial mechanical properties in muscular strength trained younger athletes with a well matched group of sedentary men. Results indicated that both the proximal aorta and arteries in the legs were stiffer in strength trained men versus the sedentary controls. Similar to the results noted in one of the aerobic training studies (Cameron et al., 1994), the differences in arterial compliance cannot be attributed to differences in mean arterial pressure but is rather likely due to intrinsic differences in the proximal aorta.

Miyachi et al. (2003) examined the interaction between age and resistance training on central arterial compliance. Carotid arterial compliance was assessed in young and middle aged men, who were either resistance trained or sedentary using a cross sectional design. Among the middle aged men, findings indicate that central arterial compliance in the resistance trained men was 30% lower than their sedentary counterparts providing support for the earlier findings of Bertovic et al. (1999). Also, age associated reductions in central arterial compliance were greater in the resistance trained versus the sedentary men. Regarding the distensibility of peripheral muscular arteries, this study found no significant differences between the groups suggesting that effect resistance training may only pertain to central arteries (Miyachi et al., 2003).

The cross sectional nature of these studies does not permit investigation of the mechanisms by which regular resistance training may decrease arterial distensibility. Perhaps the acute elevations in BP associated with resistance exercise lead to long term changes in the smooth muscle content of the arterial wall and the load bearing properties of collagen and elastin (Bertovic et al., 1999; Miyachi et al., 2003). It is clear that future studies are required to determine the physiological mechanisms underlying the influence of habitual resistance training on arterial distensibility. Moving from a cross sectional design to an interventional approach would also reduce the impact of potential confounders.

2.5.3 Isometric Exercise

No studies to date have been conducted that examine the impact of isometric exercise training on central or peripheral arterial distensibility. Given the beneficial effects of isometric exercise on resting BP (Ray & Hume, 1998; Taylor et al., 2003; Wiley et al., 1992; Buck et al., 1985; Kiveloff et al., 1971), its impact on arterial distensibility warrants investigation. Studies should address the question of whether improved arterial distensibility is a mechanism behind the reduction in BP observed with isometric training or whether arterial distensibility changes independently of a change BP.

3.0 MATERIALS AND METHODS

3.1 Subjects

The participants in the present study were recruited form the Mac Turtle Cardiac Rehabilitation Program, the Mac Senior Exercise and Wellness Program, as well as from the general public via a media campaign. The study consisted of 18 males and 6 females all of whom were medicated for essential hypertension. Mean participant age was 63 years. This and other pertinent subject information is summarized in Appendix B.

Upon showing interest in the study, participants were screened to determine if they met the inclusion criteria. The screening process consisted of a medical questionnaire that asked potential subjects about information relevant to their inclusion or exclusion from the study. To be eligible for the study, it was required that all participants currently be receiving pharmacological treatment for their hypertension. The anti-hypertensive medications the subjects were taking during the course of study are listed in Appendix B. People who were not eligible for the study included individuals with diabetes, congestive heart failure, those who smoked, and those who were receiving hormone replacement therapy.

If the inclusion criteria were met, informed, written consent was obtained from each participant. All testing and training procedures employed in the present study were approved by the McMaster University Medical Research Ethics Board and were performed in the Exercise and Metabolism Research Laboratory and the Center for Health Promotion and Rehabilitation at McMaster University.

Prior to beginning the present study, participants were randomized into either a one handed isometric handgrip exercise group (IHG), a one legged isometric leg press exercise group (ILP) or a non-exercising control group (C). The IHG contained 10 subjects, the ILP contained 9 subjects, while the control group consisted of 5 participants.

3.2 Study Design

Participants in the present study trained 3 days per week for 8 weeks. Two of these weekly exercise sessions were performed at the Center for Health Promotion and Rehabilitation at McMaster University with the assistance of a volunteer trainer. The third weekly exercise session was performed at home. Subjects were tested before training commenced, after the fourth week of training, and after the eighth week of training to determine if changes in resting BP and/or arterial distensibility occurred.

3.3 Testing Procedure

All three testing sessions, the pre, 4-week and 8-week tests, were performed in the Exercise and Metabolism Laboratory at McMaster University. Prior to their first test, all participants visited the lab and where familiarized with the procedures that would take place. All participants were informed prior to their test date that they were to refrain from performing vigorous exercise 24 hours before their test, refrain from consuming caffeine for 12 hours before their test, and refrain from eating for 4 hours before their test.

3.3.1 Assessing Heart Rate

Upon entering the lab for testing, subjects were outfitted with 2 sets of 3 electrocardiogram (ECG) electrodes in order to record a HR with two separate systems throughout the testing session. Two electrodes were placed inferiorly to the right clavicle, two were placed inferiorly to the left clavicle, and the final two were placed on the left side of the torso inferiorly to the nipple. The subsequent ECG signal from one set of electrodes was captured by the Cardiomatic (Model MSC 71233, Medical Systems Corp, USA). This signal was then sent through an analogue to digital converter (Powerlab 16sp, AD Instruments) which had a sampling rate of 100-200 Hz per second and recorded on Powerlab Chart 4 Software (AD Instruments). Data was stored on a personal computer (IBM Nevista x86 compatible processor, White Plains, USA) for future analysis. The second set of electrodes allowed for a heart rate signal to be obtained by the Doppler ultrasound (Model System Five, GE Medical Systems, USA). Data was saved both digitally and on video for future analysis.

3.3.2 Assessing Resting Blood Pressure

Resting BP was measured at the beginning of each of the three testing sessions using an automated oscillometric BP measurement device (model CBM-7000, Colin Medical Instruments, San Antonio, USA). A standard BP cuff was placed over the right brachial artery and participants were left in the supine position to rest in a quiet, temperature controlled room for 20 minutes. At 12 minutes, 14 minutes, and 16 minutes into the rest period, an investigator obtained measurements BP. These three resting SBP

and DBP values were then averaged to give one resting SBP and one resting DBP value for each of the three testing time points.

3.3.3 Assessing Common Carotid Arterial Distensibility

Distensibility of the common carotid artery was assessed in all participants, regardless of their group assignment, at each of the three testing sessions. A combination of ultrasound imaging and simultaneous applanation tonometry was used for the non-invasive determination of arterial distensibility.

Common carotid diameter was measured from images obtained by B-mode ultrasound (model System Five, GE Medical Systems, USA). A 10MHz ultrasound probe (high resolution linear array transducer) was placed over the left common carotid artery proximal to the bifurcation point. Once the near and far walls of the artery were clearly visible on the monitor, two images of the common carotid artery were taken. Each image obtained represents one heart cycle or one R-R interval. Each image was saved in a digital format and then transferred to a stacked DICOM JPEG file for later off line analysis. These images were also recoded on Super VHS videotape. All images were analyzed by the same investigator using an automatic edge detection software program (Automated Measurement System (AMS II), Chalmers University, Gotenberg, Sweden). The distances between the vessel near wall boundary, which corresponded to the interface between the adventitia and media, and the vessel far wall boundary, which corresponded to the interface of the lumen and the intima were measured. Time points that corresponded with systolic expansion (maximum diameter) and diastolic relaxation

(minimum diameter) of the common carotid artery were selected and used to determine diameter change in one heart cycle.

Simultaneous to the acquisition of ultrasound images, PP was measured in the right common carotid artery and the radial artery on a beat-by-beat basis. This non-invasive method of pressure wave measurement used is based on the principle of applanation tonometry. Upon locating the point of maximal arterial pulsation in the common carotid artery, a pencil type probe containing a high fidelity strain-gauge transducer (model SPT-301, Millar Instruments Inc., Texas, USA) was held on the skin over the site of maximal pulsation. The pencil-like probe was then pressed down on the carotid artery against underlying rigid structures. Once regular and consistent waveforms were obtained for a several cardiac beats, the pressure waves were recorded. Simultaneously to pressure waveforms being obtained in the carotid artery, they were also obtained from the radial artery using applanation tonometry (model CBM-7000, Colin Medical Instruments, San Antonio, USA). A sensor was placed over the point of maximal pulsation in the radial artery and beat-by-beat blood pressure waveforms were obtained. The signal, or pressure waveforms, obtained from both the carotid and radial arteries were passed through an analogue to digital converter (Powerlab 16sp, AD Instruments, Colorado Springs, USA) with a sampling rate of 100-200 Hz per second. The resulting digital signal was recorded on Powerlab Chart 4 software (AD Instruements,Colorado Springs USA) and saved on a personal computer (IBM Nevista x86 compatible processor, White Plains, USA) for later analysis. Simultaneous to this recording, ultrasound images of the common carotid artery were saved both digitally and

on video. The time of image acquisition was marked on the Powerlab Chart 4 software with an external trigger for future analysis.

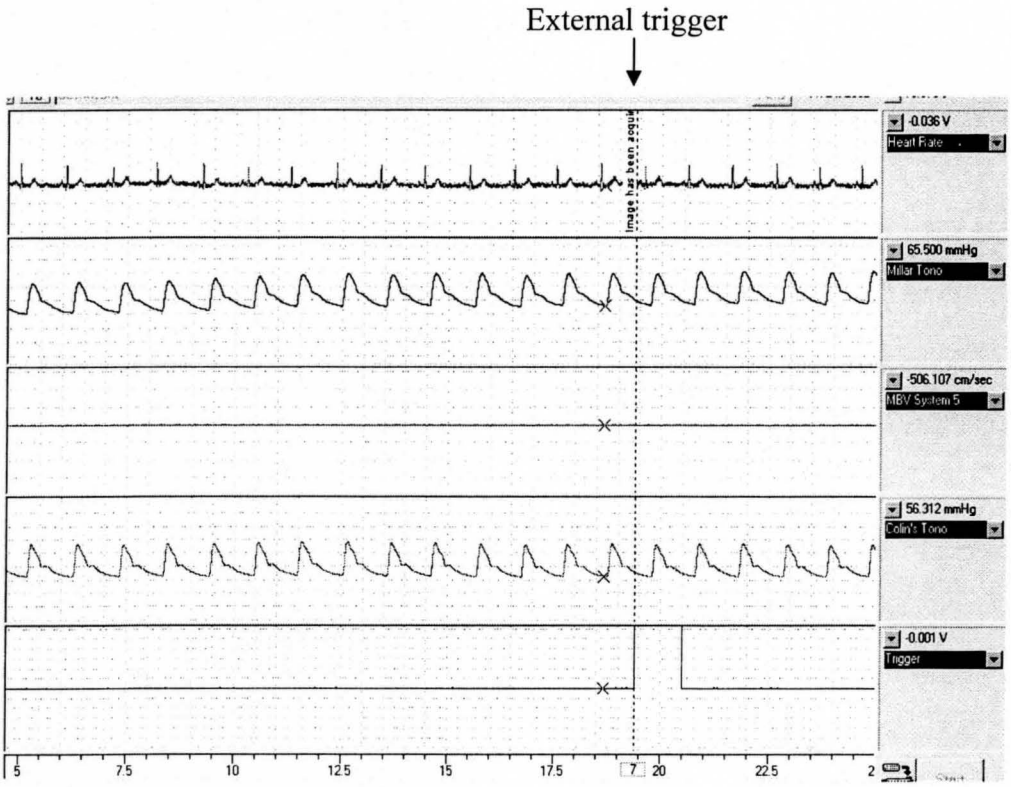

Fig 1: Powerlab data diplaying the heart rate, Millar BP (carotid tonometry) and Colin BP (radial tonometry) channels. Ultrasound image recorded is marked with the external trigger.

The pencil type probe used to assess BP in the carotid artery provided an uncalibrated pressure waveform in volts which we converted to mmHg using the radial artery pressure as a reference. The pressure signal obtained by tonometry in the carotid artery was calibrated by assigning the diastolic pressure measured by radial tonometry to

its minimum pressure value, and the mean pressure (1/3(SBP-DBP) + DBP) as assessed by radial tonometry to its average value. This procedure is based on the assumption that mean pressure does not change in large conduit arteries and that diastolic pressure is not significantly different among carotid, brachial, and femoral arteries (Kelly et al., 1989). SBP however does not remain constant between central and peripheral arteries due to pulse wave amplification as the arterial pressure wave is transmitted down the arterial tree (Izzo, Jr. et al., 2001). Therefore, to determine SBP in the carotid artery, the diastolic and mean arterial pressures obtained by radial tonometry were equated with the corresponding signal in the carotid pressure waveform. The SBP in the carotid artery was then extrapolated from this relationship (Fig 2).

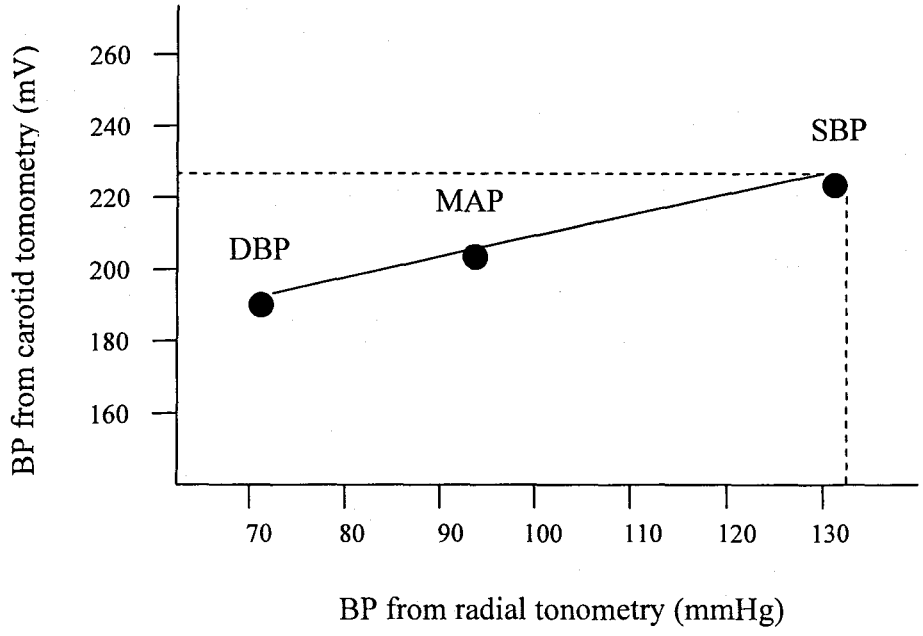

Fig 2: SBP in the carotid artery in mmHg is calculated by extrapolating from the relationship between DBP and MAP, whose values are known in both mmHg and mV.

In order to calculate the distensibility of the common carotid artery, the diameter changes (Δ D) as well as the corresponding PP values are required. Diameter change was calculated by subtracting of the minimum diameter from the maximum diameter in each of the two common carotid images.

$$\Delta D = \text{maximum diameter} - \text{minimum diameter} \qquad \text{(Equation 1)}$$

PP (Δ P) was calculated by subtracting the DBP from the SBP. The pressure waveform analyzed occurred one heart cycle prior to the trigger in the Powerlab Chart 4 Software (AD Instruments) file. This heart cycle corresponded to the image that was acquired by the Doppler ultrasound.

$$\Delta P = SBP - DBP \qquad \text{(Equation 2)}$$

Arterial distensibility was defined as the relative diameter change in an artery for a given change in pressure.

$$\text{Arterial Distensibility} = \Delta D / (\Delta P \times D) \qquad \text{(Equation 3)}$$

where D is resting diameter. The value used was minimum arterial diameter. Arterial distensibility was consequently calculated for the two images and their corresponding

pulse pressures. These two values were then averaged to give a measure of common carotid arterial distensibility at all three testing time points.

3.3.4 Assessing Exercising Limb Arterial Distensibility

Subjects in the IHG group performed the IHG exercise with their non-dominant hand. For all but one subject, this was their left hand. Distensibility of the brachial artery in the exercising limb was measured at all three testing sessions using a similar method to that which was used to assess carotid artery distensibility. Using a 10MHz ultrasound probe, 2 images of the brachial artery were obtained approximately 4cm proximal to the olecranon fossa. Simultaneously to the acquisition of the images, pulse pressure values were obtained at the brachial artery using the pencil type applanation tonometry probe and applanation tonometry at the radial artery (model CBM-7000, Colin Medical Instruments, San Antonio, USA). The pencil type probe was placed on the surface of the skin over the brachial artery distal to the ultrasound probe. Once a clear ultrasound image was obtained and the pressure waveforms were regular and consistent, the data was recorded and subsequently analyzed in the same manner as described previously for the carotid artery.

Distensibility of the left brachial artery was also assessed in the control participants at the three testing sessions. The method employed was exactly the same as that described above.

Subjects in the ILP group performed the ILP exercise with their left leg. Distensibility was measured in the femoral artery of the left leg. A 10MHz ultrasound probe was placed over the femoral artery approximately 2cm proximal to the bifurcation

point. Once again, two images were taken of the artery simultaneously to the acquisition of PP values. Due to the anatomical depth of these arteries is was not possible to use the pencil type applanation tonometry probe for the acquisition of pressure waveforms. In substitution for this, pressure waveforms were obtained by applanation tonometry at the radial artery of the left arm (model CBM-7000, Colin Medical Instruments, SanAntonio, USA). The data was recorded and analyzed according to the method previously described for both the carotid and brachial arteries.

3.3.5 Assessing Non-Exercising Limb Distensibility

In an attempt to determine if arterial distensibility changes that may occur after isometric training are local or systemic, distensibility was measured in a non-exercising limb in the IHG group, the ILP group, and the control group.

For all but one subject in the IHG group, the non-exercising limb assessed was the right arm. Distensibility was measured in the brachial artery of the non-exercising limb at all three testing sessions. The method employed was identical to that used in the measurement of brachial artery distensibility in the exercising limb of the IHG group. This procedure is described in detail above.

With regards to the ILP group, the non-exercising limb for all participants was considered their left arm. Therefore, distensibility was assessed in the left brachial artery in accordance with the method previously described for brachial artery distensibility measurements.

Finally, distensibility of the right brachial artery was measured in the control group using the method described above.

3.4 Isometric Training Procedure

The isometric training performed for the purpose of the study was in addition to any regular exercise program the participants were already involved in. Exercise log books were kept in order to ensure activity level remained consistent throughout the duration of the study. Participants in the IHG and ILP exercise groups performed isometric exercise 3 days per week for 8 weeks. Two of the exercise sessions were preformed in the Center for Health Promotion and Rehabilitation under the supervision of a student trainer. Upon arrival participants were asked to rest in an upright seated position for 5 minutes. After this rest period BP was taken using an oscillometric BP measuring device (Dinamap, PRO 100-400, Critkon Vital Answers, Tampa, FL, USA) and recorded in the subject's log book. Other items recorded in the log book included medication changes, activities performed that day, and general comments about well-being. Prior to beginning the isometric training, participants were asked to perform a low intensity warm up (either walking or cycling) for 5 minutes. The third weekly training session was carried out at home. Subjects were given a log book in which they recorded the date they trained at home, additional activities of that day, and general comments regarding health and well-being. The control group performed no exercise and visited the laboratory only for their testing sessions.

3.4.1 IHG Training Protocol

Using their non-dominant hand, subjects performed 4 isometric contractions per training session on a handgrip dynamometer (CardioGrip, MD systems, Wetserville, OH, USA). The handgrip dynamometer was programmed to carry out this specific protocol

and was equipped with a visual display to provide feedback to the participant during their training. The contractions were held for 2 minutes and followed by a 4 minute rest period. Prior to commencing the training session, the handgrip dynamometer prompted the subjects to perform a maximal voluntary handgrip contraction (MVC). This maximum score was subsequently recoded in the participant's logbook. The intensity with which the subjects trained during that session was determined as 30% of this MVC. Subjects performed this MVC at the beginning of each training session for the determination of that day's training intensity. During the isometric contractions, participants were seated with their non-dominant arm bent at the elbow and their forearm resting on a table. Student trainers motivated the participant to hold the isometric contraction at the appropriate intensity and reminded the subjects to breath normally throughout the exercise. Upon completion of each training session, the handgrip dynamometer calculated a final score out of 100 for each participant which was recoded in the log book.

3.4.2 ILP Training Protocol

Subjects performed ILP exercise with their left leg 4 times per training session. Similarly to the IHG group, these contractions were held for 2 minutes and were followed by a 4 minute rest period. Prior to commencing training, subjects performed a one repetition maximum (1RM) test on the seated leg press (Universal Gym Equipment Inc, Cedar Rapids, Iowa) in accordance with the guidelines set by the American College of Sports Medicine (2000). Training intensity was calculated as 30% of this maximal leg press. The 1RM test was performed again after 4 weeks of training and training intensity

was adjusted accordingly if necessary. In addition to the 1RM test, the training joint angle was also determined before the first training session. Subjects stood with their backs against a wall and their feet about one foot's length away from the wall. They were asked to squat down until they could no longer see their toes (i.e. their knees were above their toes). This angle was then measured using a goniometer and was considered the training angle for the duration of the study. Unlike the IHG group, the ILP group could not simply take their training apparatus home for the third weekly training session. Therefore, subjects in the ILP group performed a wall squat in substitution for the leg press exercise. Instructions regarding position during the wall squat were the same as the instructions given for the determination of the training joint angle. The four isometric wall squats performed at home were held for 2 minutes followed by 4 minutes of rest.

3.5 Statistical Analysis

Data are presented as mean ± standard error of the mean (SEM). Differences between experimental groups (IHG, ILP, and C) or time points (pre, 4wk, 8wk) were analyzed using 2-way repeated measures ANOVA for each dependant variable. Differences between selected means were investigated using the Tukey HSD post hoc method. A p-value of <0.05 was considered statistically significant.

4.0 RESULTS

4.1 Subject Characteristics

Subject descriptive characteristics are displayed in Appendix B. ANOVA and post hoc summaries are presented in Appendix C. Significant differences between the IHG, ILP and C group were noted for height ($p=0.0317$). Tukey HSD posy hoc analysis revealed specific differences between the ILP and C groups ($p=0.0268$)

4.2 Resting Blood Pressure

Analysis of SBP for the IHG, ILP, and control (C) groups at the three testing time points (pre, 4 week, and 8 week) revealed neither significant interaction effects ($p=0.167$) nor main effects for time ($p=0.485$) or group ($p=0.921$). SBP values for the IHG group are as follows; 140 ± 4.8mmHg, 135 ± 4.8mmHg, and 132 ± 5.1mmHg at the pre, 4 week, and 8 week time points respectively. SBP for the ILP group are as follows; 132 ± 5.0mmHg, 137 ± 5.0mmHg, and 136 ± 5.4mmHg at the pre, 4 week, and 8 week time points respectively. Finally, SBP values for the C group are as follows; 136 ± 6.7mmHg, 130 ± 6.8mmHg, and 131 ± 7.2mmHg at the pre, 4week, and 8 week time points respectively. SBP values for each group at pre, 4 week, and 8 week are presented in FIGURE 3.

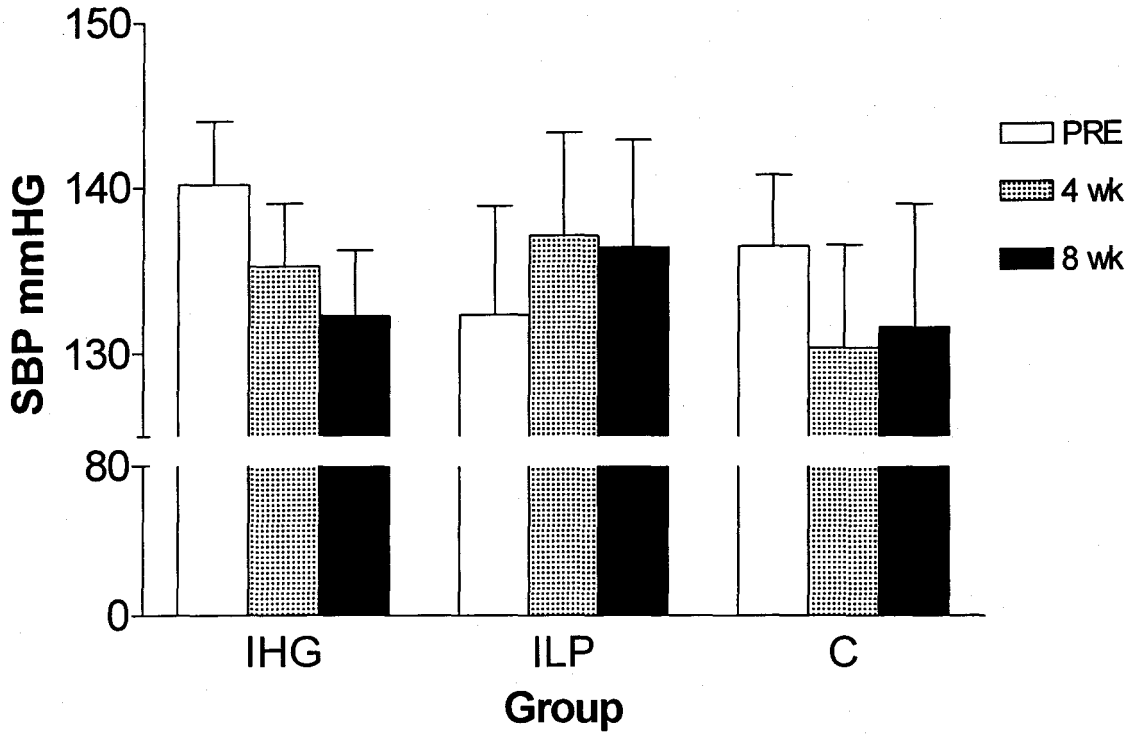

FIGURE 3: Systolic Blood Pressure (SBP) measured by brachial oscillometry in the IHG (n=10), ILP (n=9) and C (n=5). Values are plotted as mean ± SEM. No main effects of TIME (p=0.485) or GROUP (p=0.921). No significant interaction effect (p= 0.167)

Analysis of DBP for the IHG, ILP, and C groups at the three testing time points (pre, 4 week, and 8 week) showed no significant interaction effects ($p=0.29$) or main effects for group ($p=0.156$) or time ($p=0.75$). DBP values for the IHG group are as follows; 78 ± 3.5mmHg, 77 ± 3.0mmHg, and 76 ± 3.6mmHg at the pre, 4 week, and 8 week time points respectively. DBP values for the ILP group are as follows; 71 ± 3.7mmHg, 76 ± 3.2mmHg, and 73 ± 3.8mmHg at the pre, 4 week, and 8 week time points respectively. Finally, DBP values for the C group are as follows; 68 ± 5.0mmHg, 65 ± 4.3mmHg, and 65 ± 5.1mmHg at the pre, 4 week, and 8 week time points respectively. DBP values are presented in FIGURE 4.

4.3 Carotid Artery Distensibility

Carotid artery distensibility was measured in duplicate at the three testing sessions. Values reported for subjects at each testing session are the mean of the duplicate measurements.

Analysis of carotid artery distensibility values for the IHG, ILP, and C groups at pre, 4 week, and 8 week revealed a significant main effect of TIME ($p=0.028$). Tukey HSD analysis showed specific differences existed between the pre and 8 week time points ($p=0.011$). A significant main effect of group was also found ($p=0.05$). Tukey HSD analysis revealed specific difference between the IHG and ILP groups ($p=0.043$). A significant interaction ($p=0.293$) was not found. Carotid artery distensibility values for the IHG group are as follows; 0.0011 ± 0.0001 $mmHg^{-1}$, 0.0014 ± 0.0002 $mmHg^{-1}$, and 0.0016 ± 0.0004 $mmHg^{-1}$ at pre, 4 week, and 8 week respectively. Carotid artery

distensibility values for the ILP group are as follows; 0.0016 ± 0.0001 $mmHg^{-1}$, 0.0016 ± 0.0002 $mmHg^{-1}$, and 0.0029 ± 0.0004 $mmHg^{-1}$ at pre, 4 week, and 8 week respectively. Finally, the carotid artery distensibility values for the C group are as follows; 0.0014 ± 0.0002 $mmHg^{-1}$, 0.0016 ± 0.0003 $mmHg^{-1}$, and 0.0017 ± 0.0005 $mmhg^{-1}$ at pre, 4 week, and 8 week respectively. CD data at pre, 4week, and 8week are presented as mean ± SEM in FIGURE 5.

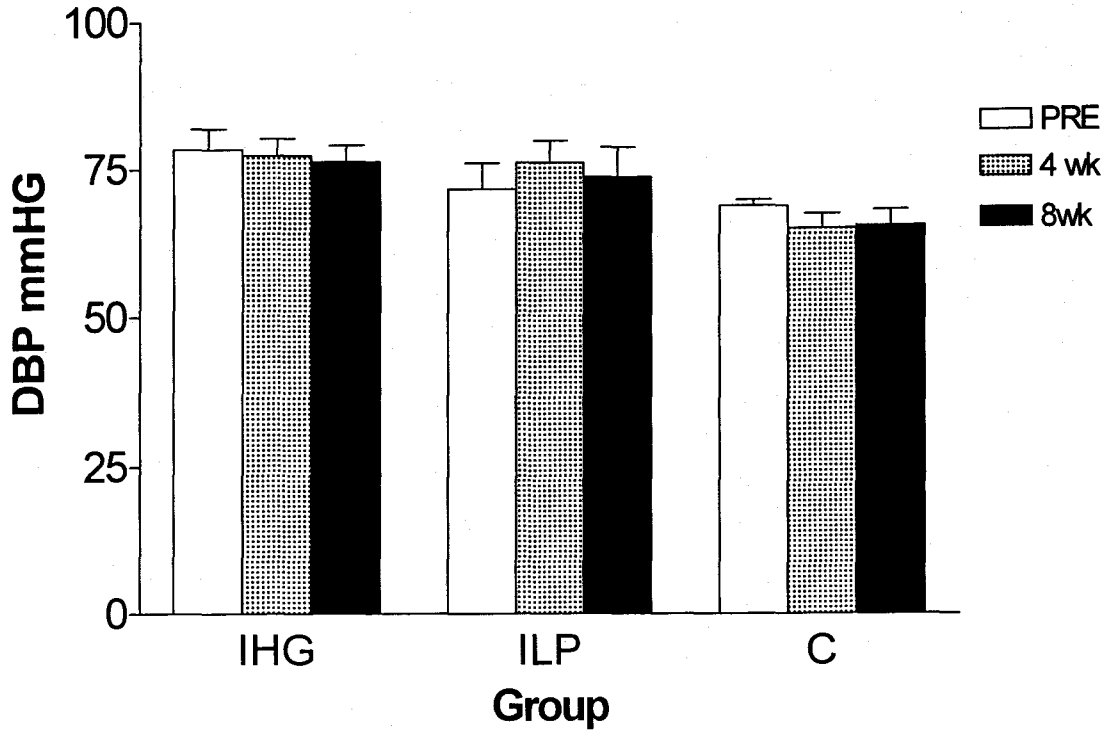

FIGURE 4: Diastolic Blood Pressure (DBP) as measured by brachial oscillometry in IHG (n=10), ILP (n=9), and C (n=5). Values are plotted as mean ± SEM. No significant main effect of GROUP (p=0.156) or TIME (p=0.75). No significant interaction effect (p=0.29)

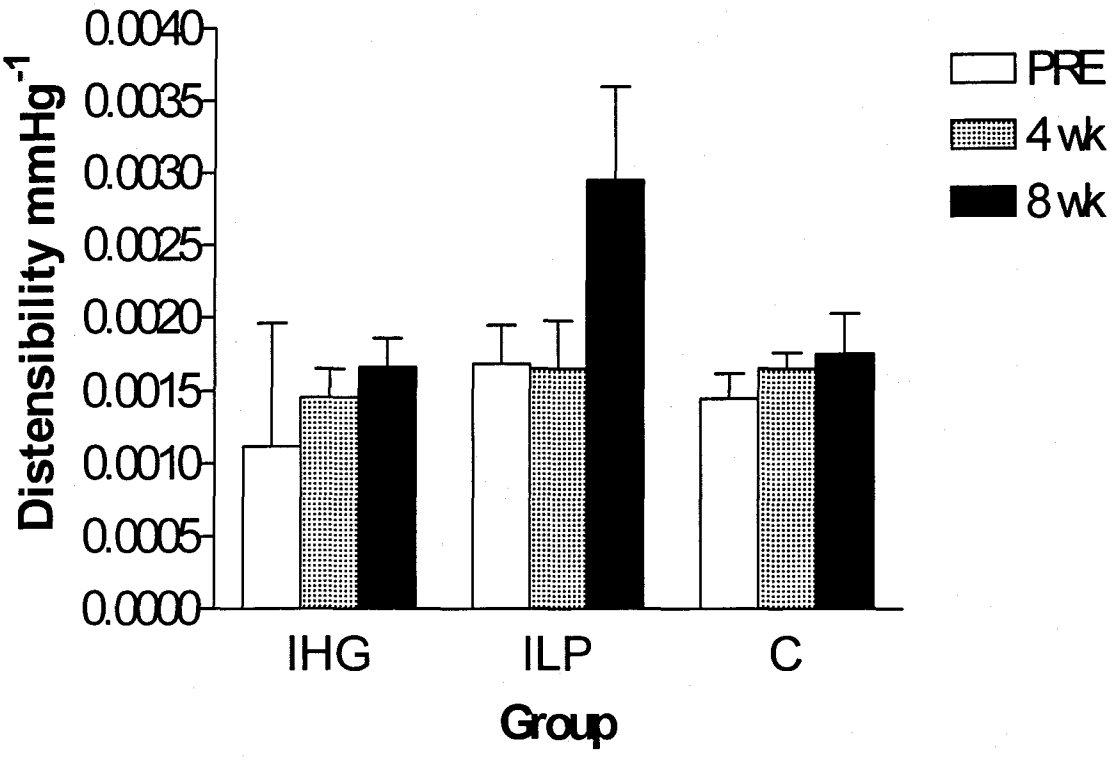

FIGURE 5: Carotid Artery Distensibility measured by combined Doppler ultrasound and applanation tonometry in IHG (n=10), ILP (n=9), and C (n=5). Values are plotted as mean ± SEM. Significant main effect of TIME ($p<0.05$). Specific differences lie between pre and 8wk. Significant main effect of GROUP ($p<0.05$). Specific differences lie between the IHG and ILP groups. No significant interaction effect ($p=0.293$).

4.4 Muscular Artery Distensibility

4.4.1 Exercising Limb

Those subjects in the IHG and C groups had distensibility assessed in their left brachial artery, while femoral artery distensibility was measured in the ILP group.

Analysis of exercising limb distensibility values for the IHG, ILP, and C groups at pre, 4 week, and 8 week yielded a significant main effect of GROUP ($p=0.026$). After a Tukey HSD post hoc test, specific differences were found between the IHG and ILP groups ($p=0.021$). There was no significant interaction effect ($p=0.333$) or main effect of time ($p=0.683$) for this measure. Values for the IHG group are as follows; 0.0007 ± 0.0002 $mmHg^{-1}$, 0.0009 ± 0.0001 $mmHg^{-1}$, and 0.0007 ± 0.0004 $mmHg^{-1}$ at pre, 4 week, and 8 week respectively. Values for the ILP group are as follows; 0.0014 ± 0.0002 $mmHg^{-1}$, 0.0009 ± 0.0001 $mmHg^{-1}$, and 0.0019 ± 0.0004 $mmHg^{-1}$ at pre, 4 week, and 8 week respectively. Finally, values for the C group are as follows; 0.0009 ± 0.0002 $mmHg^{-1}$, 0.0015 ± 0.0002 $mmHg^{-1}$, and 0.0011 ± 0.0005 $mmHg^{-1}$ at pre, 4 week, and 8 week respectively. Exercising limb distensibility values can be found in FIGURE 6.

4.4.2 Non-Exercising Limb

Distensibility was assessed in the right brachial artery of those the IHG and C groups. Individuals in the ILP group had distensibility measured in their left brachial artery.

Analysis of non-exercising limb distensibility for the IHG, ILP, and C groups at pre, 4 week, and 8 week revealed no significant interaction ($p=0.487$) or main effects for time ($p=0.52$) or group ($p=0.87$). Values for the IHG group are as follows; $0.0007 \pm$

0.00009 $mmHg^{-1}$, 0.0008 ± 0.0001 mmHg-^{1}, and 0.0008 ± 0.0001 $mmHg^{-1}$ at pre, 4 week, and 8 week respectively. Values for the ILP group are as follows; 0.0009 ± 0.0001 $mmHg^{-1}$, 0.0008 ± 0.0001 $mmHg^{-1}$, and 0.0008 ± 0.0001 $mmHg^{-1}$ at pre, 4 week ,and 8 week respectively. Finally, values for the C group are as follows; 0.0006 ± 0.0001 $mmHg^{-1}$, 0.001 ± 0.0002 $mmHg^{-1}$, and 0.0009 ± 0.0001 $mmHg^{-1}$ at pre, 4 week, and 8 week respectively. Non-exercising limb distensibility values are displayed in FIGURE 7.

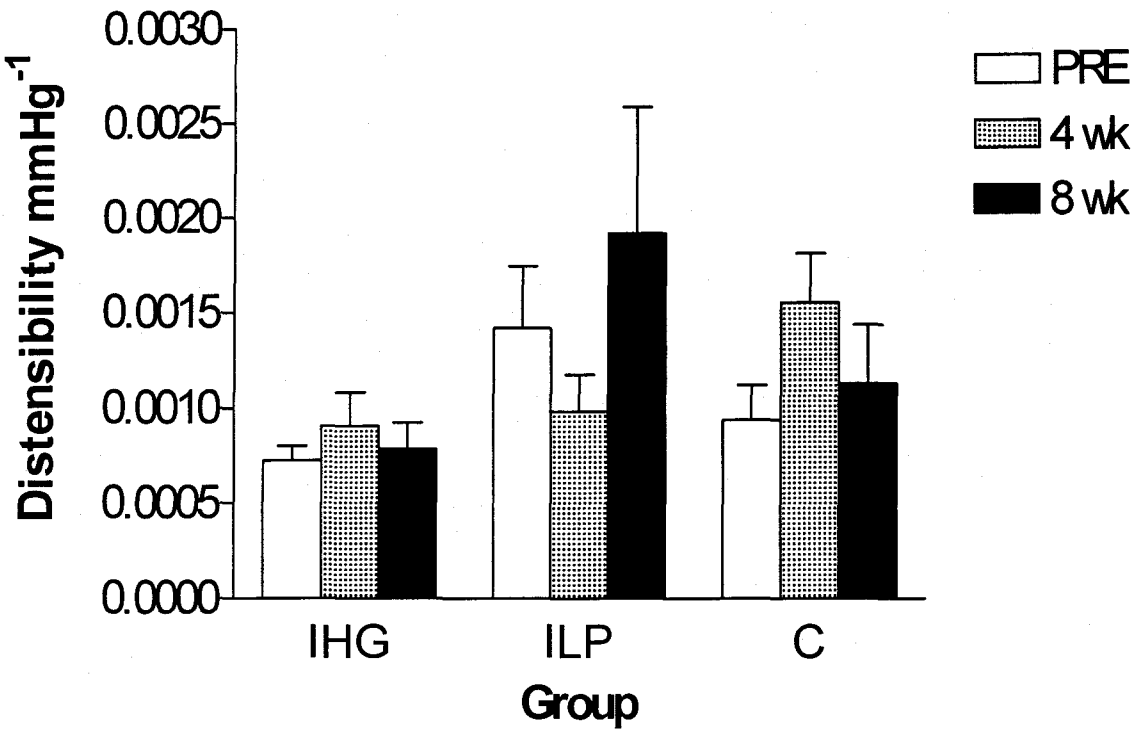

FIGURE 6: Exercising Limb Distensibility measured by Doppler ultrasound and applanation tonometry in IHG (n=10), ILP (n=9) and C (n=5). Significant main effect of GROUP (p=0.026). Specific differences lie between IHG and ILP. No significant main effect of time (p=0.683). No significant interaction effect (p=0.333).

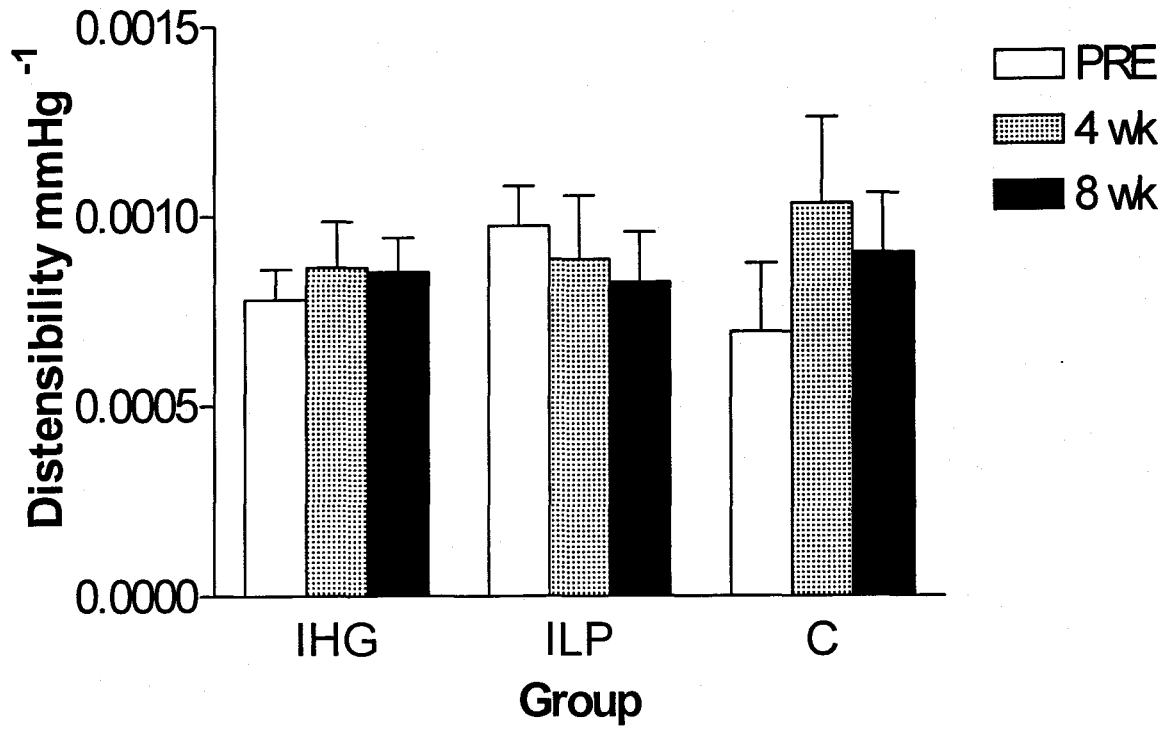

FIGURE 7: Non-exercising Limb Distensibility measured by Doppler ultrasound and applanation tonometry in IHG (n=10), ILP (n=9) and C (n=5). No significant effect of GROUP (p=0.87) or TIME (p=0.52). No significant interaction effect (p=0.487).

5.0 DISCUSSION

The purpose of the present study was threefold: 1) to reproduce the BP lowering effects of IHG training in persons medicated for hypertension, 2) to compare IHG and ILP based on their BP lowering effects, and 3) to determine whether IHG or ILP exercise modified arterial distensibility. Contrary to our hypothesis, neither IHG nor ILP significantly reduced BP when compared to the control group. Also, neither central nor peripheral arterial distensibility were improved by IHG or ILP training.

5.1 Reproduction of BP Lowering Effect of IHG

This is the first study to examine IHG and not demonstrate a significant reduction in either SBP or DBP. Wiley et al. employed an almost identical training protocol to the one used in this study and found SBP and DBP to decrease by 12.5 and 14.9 mmHg respectively (Wiley et al., 1992). Wiley et al. examined young and healthy people with borderline hypertension. The hypertension disease process in this population may have been in its beginning stages perhaps making them more receptive to the IHG stimulus. Also, measures of resting BP were taken after 10 minutes of seated rest by auscultation using a standard sphygmomanonmeter. As compared to the automated oscillometric technique used in the present study, this method is susceptible to observer error.

Following a slightly shorter and more intense IHG training program, DBP decreased by 5mmHg while MAP decrease by 4mmHg (Ray et al., 2000). As opposed to the present study which examined older, medicated hypertensives, this study investigated young, healthy, normotensive subjects. The protocol used by Ray et al. was similar to the

one employed in the present study. However, the notable absence of hypertension in the subjects makes if difficult to directly compare results.

Other studies that have shown a BP reduction following IHG training used an alternating hand protocol (Taylor et al., 2003). This protocol distributed the pressor stimulus to two vascular beds as opposed to only one vascular bed in the present study. Enhancing the size of the vascular beds affected may facilitate the blood pressure lowering effect. Taylor et al. (2003) noted significant reductions in SBP and MAP after 10 weeks of IHG training. Perhaps the present studied needed to be longer in duration to detect significant reductions in SBP and/or DBP. Despite the incongruence in study duration and protocol, both studies investigated older persons with medicated hypertension. This perhaps forms the most important basis for comparison.

Limitations to the present study exist that may have hindered our ability to demonstrate significant BP reductions. Most importantly, the control group was half the size of the IHG group. When the data was analyzed in a one way ANOVA without the control group, significant BP reductions were noted in the IHG group. However, when compared to the small and variable control group, the significant effect is lost. The small size of the control group may have lead to a Type 2 error whereby we concluded that IHG was ineffective at lowering BP when in fact it was effective.

The present study controlled for a number of factors known to influence BP. All three testing sessions were performed at the same time of day in a quiet and dimmed room. Also, food ingestion, caffeine consumption, and exercise prior to the testing

session were controlled. Despite these strict controls, certain factors including emotional disturbances or fatigue may have compromised the results.

5.2 BP Response to IHG and ILP Exercise Training

The present study was the first to examine the effect of ILP training on BP. As mentioned above, all of the randomized controlled trials examining isometric exercise and BP have used handgrip exercise. In the present study, ILP training did not lower resting BP when compared to the control or IHG groups. In fact, when considered independently of the control and IHG groups, the ILP group did not demonstrate any trend toward lower BP following the 8 weeks of training.

A direct relationship exists between the size of the active muscle mass and the magnitude of the increase in MAP, even when contractions are performed at the same relative intensity (Seals et al., 1983). This evidence provided the rationale for examining ILP exercise. If an IHG contraction at 30% MVC elicited a given pressor response then an ILP contraction at 30% MVC is assumed to elicit an even greater response. It would have been valuable to examine the acute BP response to IHG and ILP exercise at 30% MVC. This would allow for the characterization of the cardiovascular response to the specific stimuli used in the present study. Based on the literature, it was hypothesized that an even greater reduction in resting BP would follow ILP exercise training versus IHG training. This however, was not the case, with ILP training failing to significantly alter resting BP and not providing greater reductions than the IHG group.

This unpredicted result may have occurred for a number of reasons. Although every attempt was made to equate the IHG and ILP training protocols, some differences did exist. Recall that participants trained with a load equivalent to 30% of their MVC. The IHG group performed a 1RM test at the beginning of each training session to determine their training load for that session. However, the ILP group had their 1RM assessed prior to beginning the training protocol and again after 4 weeks of training. Therefore, those in the ILP group may not have been receiving an adequate training stimulus at each session. Ideally, an evaluation of maximum strength should have been performed prior to each session for the ILP group as well. However, due to the time needed to properly perform a 1RM test this was simply not feasible. Also, the 1RM test used for the IHG group was a measure of isometric strength while the 1RM test for the ILP group was a measure of dynamic strength. The use a force transducer plate would have been more effective for the assessment of isometric strength in the ILP group.

A second difference between the IHG and ILP groups was the nature of the third, at home exercise session. The exercise the IHG group performed at home was identical to that performed in the exercise center. The ILP group however, could not take the leg press machine home and had to perform a wall squat instead. The load the subjects were training with at home session was not standardized at all. In fact, it is likely that the stimulus may have been substantially greater than 30% MVC as the subjects were supporting all of their body weight on their left leg. Perhaps this third at home session could have been considered a more intense and vigorous form of training. Data from intense resistance training studies and its impact on resting BP are equivocal. When

compared to aerobic (Pescatello et al., 2004) and more recently IHG exercise (Ray et al., 2000; Taylor et al., 2003; Wiley et al., 1992), resistance training does not seen to have the same BP lowering effect (Van Hoof et al., 1996). Perhaps the stimulus experienced by the ILP group during the at home session was physiologically different from that experienced during the other sessions and therefore was not effective at lowering resting BP.

5.3 Impact of IHG or ILP Exercise Training on Arterial Distensibility

The present study is the first to examine the effect of isometric exercise training on arterial distensibility. No changes were seen in central arterial distensibility, exercising limb distensibility, or non-exercising limb distensibility following IHG or ILP training.

The literature at present has only examined the impact of aerobic and dynamic resistance training on arterial distensibility. Based on the results of both cross sectional and interventional studies, it appears that regular aerobic exercise has the ability to improve arterial distensibility. The studies that have demonstrated such improvements however, have examined mainly central elastic arteries (Cameron et al., 1994; Kingwell et al., 1997; Schmidt-Trucksass et al., 1999; Tanaka et al., 1998; Tanaka et al., 2000; Vaitkevicius et al., 1993). The mechanism behind this improvement is only speculative. It is thought that the increased PP and mechanical distension that occur during an exercise session stretch collagen fibers and decrease their cross linking. This change in collagen cross linking would in turn increase distensibility. Arterial distensibility may

also be modified by a withdrawal of sympathetic tone from smooth muscle cells in the arterial wall (Tanaka et al., 2000).

Studies that have examined resistance training and arterial distensibility have been cross sectional in nature to date. The results appear to indicate that resistance training contributes to decreased central and peripheral arterial distensibility (Bertovic et al., 1999; Miyachi et al., 2003). A likely explanation for this may be that the acute, intermittent, and dramatic elevations in BP incurred during resistance training (MacDougall et al., 1985) may result in chronic increases in smooth muscle content of the arterial wall and the load bearing properties of collagen and elastin. It has also been proposed that resistance trained individuals have higher sympathetic nervous system activity thereby providing chronic restraint on the arterial wall through greater vasoconstrictor tone (Bertovic et al., 1999; Miyachi et al., 2003).

Because the training protocols used in the above aerobic and resistance training studies do not resemble the one used in the present study it is difficult to compare results. Given that the studies involving resistance training were cross sectional and examined people who had been strength training most of their life they do not provide an appropriate reference. Also, aerobic exercise has been known to place a volume load on the cardiovascular system as opposed to the pressure load that is the result of isometric training. Therefore, the physiological responses to these two types of exercise are different, which limits the basis for comparison.

Arterial stiffness is associated with a number of structural changes such as increases in elastin fragmentation, decreases in elastin density, and increases in collagen

concentration and density (Seals, 2003). It is possible that the rapid increases in BP induced by each isometric contraction may reverse some of these changes through intermittent stretching of the arterial wall. This stretching may lead to increased distensibility through a synthesis or repair of elastin and/or decrease in collagen density (Seals, 2003).

In addition to the structural determinants of arterial distensibility, functional factors also play a role. The contractile state of the vascular smooth muscle is also an important determinant of arterial distensibility. The rapid increase in BP resulting from isometric contractions increases the shear stress experienced by the vessels as a results of increase in blood flow. Shear stress has been known to increase the release of endothelium-derived NO, a potent vasodilator (Sherman, 2000). Improved endothelium dependant vasodilation should suppress vascular smooth muscle tone in the arterial wall and hence improve distensibility (Seals, 2003). The tone of the vascular smooth muscle is also influenced by the sympathetic nervous activity. Evidence regarding the impact of isometric exercise and sympathetic activity remains equivocal (Ray et al., 2000; Taylor et al., 2003). If however, sympathetic activity is modified by isometric exercise, this may be one mechanism through which arterial distensibility is improved.

Despite the evidence above, it is possible that arterial distensibility is simply not modified by isometric exercise training in hypertensives. Following an 8 week program of aerobic exercise, distensibilty did not improve in people with isolated systolic hypertension (Ferrier et al., 2001).

Certain limitations to the present study may have obstructed the observation of significant findings. Recall that arterial distensibility was based on the measurement of pressure and diameter change in a given artery. Error in the measurement of PP and diameter change may have occurred in the present study. It is documented that excess pressure from the ultrasound transducer may distort the image of the artery and hence underestimate diameter change. Many participants in the present study had significant amounts of adipose tissue in their neck. Therefore, the carotid artery was quite deep and excess pressure was placed on the ultrasound transducer to obtain an image (Arnett et al., 1994). Also, the tonometry probe which was used for the determination of pulse pressure produces distorted pressure waves when a considerable amount of overlying tissue is present (Armentano et al., 1995). Finally, due to the beat by beat variability in BP, it may have been more accurate to average BP for several beats surrounding the image as opposed to taking only one BP measurement as in the present study.

In addition to measurement error, it is also possible that the training stimulus used in the present study was not sufficient to induce changes in arterial distensibility. After examining a hypertensive population following only 8 weeks of aerobic training, Ferrier et al. (2001) did not see improvements in distensibility. The only interventional study to observe improved arterial distensibility employed a three month aerobic training protocol which examined healthy individuals (Tanaka et al., 2000). Perhaps when investigating a hypertensive population a longer training program is required to improve arterial distensibility. The mechanisms that underlie increased distensibility may involve the structural remodeling of elastin and/or collagen and a functional change in the

vasoconstrictor tone exerted by the smooth muscle cells (Tanaka et al., 2000). It is not likely that these structural modifications will take place quickly. Also, in hypertensive populations who already have compromised distensibility, it may take even longer to see improvements. Hence, the results reported by Ferrier et al. (2001) suggest that individuals with hypertension may be resistant to modification through short term training.

A final factor that may have obstructed the observation of significant improvements in distensibility is that all of the participants in this study were being medicated for their hypertension. It is known that certain anti-hypertensive drugs, including ACE inhibitors, calcium channel blockers, and nitrates, can improve arterial distensibility (Dart and Kingwell, 2001). Therefore, it is possible that this population may not have had the capacity to demonstrate further improvements in distensibility following IHG or ILP training.

5.4 Potential Mechanisms

It is possible that the blood pressure reductions noted in previous studies can be attributed to mechanisms other than improved distensibility. Alternate mechanisms which have received attention include decreases in sympathetic nerve activity (Ray et al., 2000; Sinoway et al., 1996; Somers et al., 1992), improved endothelial function (Sherman, 2000; Sinoway et al., 1987), and baroreceptor resetting (Hunt et al., 2001; Monahan et al., 2001).

Eight young and healthy volunteers performed unilateral isometric handgrip training at 33% MVC for six weeks. Using measurements of MSNA it was found that IHG training caused an attenuation of sympathetic nerve activity (Somers et al., 1992). The authors suggest that this decrease is perhaps due to a decrease in muscle chemoreflex stimulation. Muscle chemosensitive afferents respond to metabolic products of ischemic exercise. Stimulation of the muscle chemoreflex is a powerful stimulus for the activation of sympathetic nerve activity. In addition to isometric handgrip exercise, rhythmic forearm training has also been proven to attenuate sympathetic nerve activity (Sinoway et al., 1996). A recent study by Taylor et al. (2003) demonstrated an increase in vagal modulation of the autonomic nervous system as assessed via HR and BP variability following IHG training in addition to observing significant BP reductions. These studies suggest that a reduction in sympathetic outflow may be responsible for BP reduction seen following IHG training.

Isometric exercise may stimulate a reduction in BP through an improvement in endothelial function. Exercise causes an increase in shear stress, leading to flow-mediated dilation, which is the normal arterial response to increased blood flow. Flow mediated vasodilation depends on the presence of an intact endothelium and is mediated by the release of NO (Sherman, 2000). Following 4 weeks of handgrip exercise, forearm blood flow increased. This increased blood flow was associated with an enhanced vascular vasodilatory capacity (Sinoway et al., 1987). This adaptation may explain the BP reductions observed in other studies following isometric training.

Arterial baroreceptors are reset when their afferent nerve activity is reduced at an equivalent arterial pressure and vascular stretch. Resetting occurs as a result of stretch of the baroreceptors, usually during an acute or chronic rise in arterial pressure. It may be seen after brief exposure to a sustained elevation of pressure (acute resetting) and after chronic elevation of pressure or in physiologic or pathologic states associated with structural changes in the vascular regions of baroreceptors (chronic resetting) (Chapleau, Hajduczok, & Abboud, 1988). In patients with hypertension, carotid arterial compliance is abnormal and arterial baroreflex function is attenuated (Lage, Polak, O'Leary, & Creager, 1993). Exercise however is proven to improve central arterial compliance (Tanaka et al., 2000) as well as arterial baroreflex sensitivity (Monahan et al., 2001; Silva et al., 1997; Hunt et al., 2001). Therefore, if isometric exercise were able to improve distensibility of the carotid artery, baroreceptor sensitivity may also increase, thus causing a reduction in BP through a reduction in sympathetic outflow. Due to this potential sustained reduction in BP, the baroreceptors may reset and increase their activity at a given pressure and vascular stretch.

5.5 Summary

Contrary to our hypothesis, an 8 week isometric training program was unable to reduce BP in older adults medicated for hypertension. We were unable to reproduce the BP reductions seen with IHG training in previous studies (Taylor et al., 2003). This may have been due to the unilateral handgrip program used or due to the small and variable control group.

Despite the involvement of a larger muscle mass, ILP exercise did not reduce BP to a greater extent when compared to the IHG group. In fact, when considered independently of the control and IHG groups, the ILP group did not demonstrate any trend toward lower BP following the 8 weeks of training. Perhaps the incongruence between the IHG and ILP programs contributed the insignificant findings.

The present study was the first to examine the impact of isometric exercise training on central and peripheral artery distensibility. Neither the IHG nor ILP group was able to improve distensibility when compared to the control group. Measurement error associated with the acquisition and analysis of the ultrasound images and the use of the tonometry probe may have prevented the observation of significant changes. Previous research indicates that aerobic training can beneficially modify central artery distensibility (Cameron et al., 1994; Schmidt-Trucksass et al., 1999; Tanaka et al., 1998; Tanaka et al., 2000; Vaitkevicius et al., 1993), while resistance training has no impact on arterial distensibility (Bertovic et al., 1999; Miyachi et al., 2003). The physiological response to isometric training is more similar to that observed with resistance exercise

versus aerobic exercise. Therefore, central and peripheral artery distensibility may not be modified with isometric training.

5.6 Future Directions

A major limitation of the present study was the small size of the control group. It would prove useful to increase the size of the control group and perhaps analyse the data with equal sample sizes in each of the groups. Efforts are currently underway to recruit and test control subjects for this study.

The impact of ILP exercise or other isometric exercises involving a large muscle mass still requires investigation. As mentioned earlier, this is the first randomized controlled trial to examine ILP and its impact on BP and arterial distensibility. By equating the protocols used by the IHG and ILP groups more carefully, significant differences may have been found.

This was the first study to study the impact of isometric exercise on arterial distensibility. Although significant effects were not found, arterial distensibility should not be abandoned as a potential mechanism underlying BP reductions. Future studies should continue to examine central, perhaps aortic, distensibility as well as other mechanism which have been proposed.

The study of isometric exercise and BP is in its infancy. More studies are required to determine the optimal isometric protocol that will elicit the greatest reduction in BP. Hopefully, with continued study, isometric training will be used as an adjunct to, and possibly independently of, pharmacological treatment for hypertension.

REFERENCE LIST

2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension (2003). J.Hypertens., 21, 1983-1992.

Abboud, F. M. (1982). The sympathetic system in hypertension. State-of-the-art review. Hypertension, 4, 208-225.

American College of Sports Medicine (2000). ACSM's Guidelines for Exercise Testing and Prescription. Baltimore, Maryland: Williams and Wilkins,

Arcaro, G., Laurent, S., Jondeau, G., Hoeks, A. P., & Safar, M. E. (1991). Stiffness of the common carotid artery in treated hypertensive patients. J.Hypertens., 9, 947-954.

Armentano, R., Megnien, J. L., Simon, A., Bellenfant, F., Barra, J., & Levenson, J. (1995). Effects of hypertension on viscoelasticity of carotid and femoral arteries in humans. Hypertension, 26, 48-54.

Arnett, D. K., Evans, G. W., & Riley, W. A. (1994). Arterial stiffness: a new cardiovascular risk factor? Am.J.Epidemiol., 140, 669-682.

Benetos, A., Laurent, S., Asmar, R. G., & Lacolley, P. (1997a). Large artery stiffness in hypertension. J.Hypertens.Suppl, 15, S89-S97.

Benetos, A., Rudnichi, A., Safar, M., & Guize, L. (1998). Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension, 32, 560-564.

Benetos, A., Safar, M., Rudnichi, A., Smulyan, H., Richard, J. L., Ducimetieere, P., & Guize, L. (1997b). Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension, 30, 1410-1415.

Benetos, A., Waeber, B., Izzo, J., Mitchell, G., Resnick, L., Asmar, R., & Safar, M. (2002). Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. Am.J.Hypertens., 15, 1101-1108.

Bertovic, D. A., Waddell, T. K., Gatzka, C. D., Cameron, J. D., Dart, A. M., & Kingwell, B. A. (1999). Muscular strength training is associated with low arterial compliance and high pulse pressure. Hypertension, 33, 1385-1391.

Blair, S. N., Kohl, H. W., III, Paffenbarger, R. S., Jr., Clark, D. G., Cooper, K. H., & Gibbons, L. W. (1989). Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA, 262, 2395-2401.

Buck, C. & Donner, A. P. (1985). Isometric occupational exercise and the incidence of hypertension. J.Occup.Med., 27, 370-372.

CACR (1999). Canadian Guidelines for Cardiac Rehabilitation and Cardiovascular Disease Prevention. Winnepeg, Manitoba: Canadian Association of Cardiac Rehabilitation.

Cameron, J. D. & Dart, A. M. (1994). Exercise training increases total systemic arterial compliance in humans. Am.J.Physiol, 266, H693-H701.

Chapleau, M. W., Hajduczok, G., & Abboud, F. M. (1988). Mechanisms of resetting of arterial baroreceptors: an overview. Am.J.Med.Sci., 295, 327-334.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., Jones, D. W., Materson, B. J., Oparil, S., Wright, J. T., Jr., & Roccella, E. J. (2003). Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension, 42, 1206-1252.

Ciccone, C. D. (1996). Current trends in cardiovascular pharmacology. Phys.Ther., 76, 481-497.

Dampney, R. A., Coleman, M. J., Fontes, M. A., Hirooka, Y., Horiuchi, J., Li, Y. W., Polson, J. W., Potts, P. D., & Tagawa, T. (2002). Central mechanisms underlying short- and long-term regulation of the cardiovascular system. Clin.Exp.Pharmacol.Physiol, 29, 261-268.

Dart, A. M. & Kingwell, B. A. (2001). Pulse pressure--a review of mechanisms and clinical relevance. J.Am.Coll.Cardiol., 37, 975-984.

DeSouza, C. A., Shapiro, L. F., Clevenger, C. M., Dinenno, F. A., Monahan, K. D., Tanaka, H., & Seals, D. R. (2000). Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. Circulation, 102, 1351-1357.

Edwards, M. T. & Diana, J. N. (1978). Effect of exercise on pre- and postcapillary resistance in the spontaneously hypertensive rat. Am.J.Physiol, 234, H439-H446.

Faury, G. (2001). Function-structure relationship of elastic arteries in evolution: from microfibrils to elastin and elastic fibres. Pathol.Biol.(Paris), 49, 310-325.

Ferrier, K. E., Waddell, T. K., Gatzka, C. D., Cameron, J. D., Dart, A. M., & Kingwell, B. A. (2001). Aerobic exercise training does not modify large-artery compliance in isolated systolic hypertension. Hypertension, 38, 222-226.

Franklin, S. S., Gustin, W., Wong, N. D., Larson, M. G., Weber, M. A., Kannel, W. B., & Levy, D. (1997). Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation, 96, 308-315.

Gasowski, J., Fagard, R. H., Staessen, J. A., Grodzicki, T., Pocock, S., Boutitie, F., Gueyffier, F., & Boissel, J. P. (2002). Pulsatile blood pressure component as predictor of mortality in hypertension: a meta-analysis of clinical trial control groups. J.Hypertens., 20, 145-151.

Guyton, A. & Hall, J. (1996). Textbook of Medical Physiology. Philidelphia, Pennsylvania: W.B. Saunders Company.

Haapanen, N., Miilunpalo, S., Vuori, I., Oja, P., & Pasanen, M. (1997). Association of leisure time physical activity with the risk of coronary heart disease, hypertension and diabetes in middle-aged men and women. Int.J.Epidemiol., 26, 739-747.

Harris, K. A. & Holly, R. G. (1987). Physiological response to circuit weight training in borderline hypertensive subjects. Med.Sci.Sports Exerc., 19, 246-252.

Higashi, Y., Sasaki, S., Kurisu, S., Yoshimizu, A., Sasaki, N., Matsuura, H., Kajiyama, G., & Oshima, T. (1999a). Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide. Circulation, 100, 1194-1202.

Higashi, Y., Sasaki, S., Sasaki, N., Nakagawa, K., Ueda, T., Yoshimizu, A., Kurisu, S., Matsuura, H., Kajiyama, G., & Oshima, T. (1999b). Daily aerobic exercise improves reactive hyperemia in patients with essential hypertension. Hypertension, 33, 591-597.

Hunt, B. E., Farquhar, W. B., & Taylor, J. A. (2001). Does reduced vascular stiffening fully explain preserved cardiovagal baroreflex function in older, physically active men? Circulation, 103, 2424-2427.

Hurley, B. F., Hagberg, J. M., Goldberg, A. P., Seals, D. R., Ehsani, A. A., Brennan, R. E., & Holloszy, J. O. (1988). Resistive training can reduce coronary risk factors without altering VO2max or percent body fat. Med.Sci.Sports Exerc., 20, 150-154.

Izzo, J. L., Jr. & Shykoff, B. E. (2001). Arterial stiffness: clinical relevance, measurement, and treatment. Rev.Cardiovasc.Med., 2, 29-40.

Kannel, W. B. (1996). Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA, 275, 1571-1576.

Kaplan, R., Sallis, J., & Patterson, T. (1993). Health and Human Behavior. New York: McGraw Hill Inc.

Kelley, G. A. & Kelley, K. S. (2000). Progressive resistance exercise and resting blood pressure : A meta-analysis of randomized controlled trials. Hypertension, 35, 838-843.

Kelley, G. A. & Sharpe, K. K. (2001). Aerobic exercise and resting blood pressure in older adults: a meta-analytic review of randomized controlled trials. J.Gerontol.A Biol.Sci.Med.Sci., 56, M298-M303.

Kelly, R., Hayward, C., Avolio, A., & O'Rourke, M. (1989). Noninvasive determination of age-related changes in the human arterial pulse. Circulation, 80, 1652-1659.

Kingwell, B. A., Berry, K. L., Cameron, J. D., Jennings, G. L., & Dart, A. M. (1997). Arterial compliance increases after moderate-intensity cycling. Am.J.Physiol, 273, H2186-H2191.

Kiveloff, B. & Huber, O. (1971). Brief maximal isometric exercise in hypertension. J.Am.Geriatr.Soc., 19, 1006-1012.

Lage, S. G., Polak, J. F., O'Leary, D. H., & Creager, M. A. (1993). Relationship of arterial compliance to baroreflex function in hypertensive patients. Am.J.Physiol, 265, H232-H237.

Lanfranchi, P. A. & Somers, V. K. (2002). Arterial baroreflex function and cardiovascular variability: interactions and implications. Am.J.Physiol Regul.Integr.Comp Physiol, 283, R815-R826.

Lohmeier, T. E. (2001). The sympathetic nervous system and long-term blood pressure regulation. Am.J.Hypertens., 14, 147S-154S.

MacDonald, J. R. (2002). Potential causes, mechanisms, and implications of post exercise hypotension. J.Hum.Hypertens., 16, 225-236.

MacDougall, J. D., Tuxen, D., Sale, D. G., Moroz, J. R., & Sutton, J. R. (1985). Arterial blood pressure response to heavy resistance exercise. J.Appl.Physiol, 58, 785-790.

McCartney, N. (1998). Role of resistance training in heart disease. Med.Sci.Sports Exerc., 30, S396-S402.

McVeigh, G. E., Bratteli, C. W., Morgan, D. J., Alinder, C. M., Glasser, S. P., Finkelstein, S. M., & Cohn, J. N. (1999). Age-related abnormalities in arterial compliance

identified by pressure pulse contour analysis: aging and arterial compliance. Hypertension, 33, 1392-1398.

Miyachi, M., Donato, A. J., Yamamoto, K., Takahashi, K., Gates, P. E., Moreau, K. L., & Tanaka, H. (2003). Greater age-related reductions in central arterial compliance in resistance-trained men. Hypertension, 41, 130-135.

Monahan, K. D., Tanaka, H., Dinenno, F. A., & Seals, D. R. (2001). Central arterial compliance is associated with age- and habitual exercise-related differences in cardiovagal baroreflex sensitivity. Circulation, 104, 1627-1632.

Mostoufi-Moab, S., Widmaier, E. J., Cornett, J. A., Gray, K., & Sinoway, L. I. (1998). Forearm training reduces the exercise pressor reflex during ischemic rhythmic handgrip. J.Appl.Physiol, 84, 277-283.

Neal, B., MacMahon, S., & Chapman, N. (2000). Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet, 356, 1955-1964.

Oliver, J. J. & Webb, D. J. (2003). Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. Arterioscler.Thromb.Vasc.Biol., 23, 554-566.

Paffenbarger, R. S., Jr., Wing, A. L., Hyde, R. T., & Jung, D. L. (1983). Physical activity and incidence of hypertension in college alumni. Am.J.Epidemiol., 117, 245-257.

Pescatello, L. S., Fargo, A. E., Leach, C. N., Jr., & Scherzer, H. H. (1991). Short-term effect of dynamic exercise on arterial blood pressure. Circulation, 83, 1557-1561.

Pescatello, L. S., Franklin, B. A., Fagard, R., Farquhar, W. B., Kelley, G. A., & Ray, C. A. (2004). American College of Sports Medicine position stand. Exercise and hypertension. Med.Sci.Sports Exerc., 36, 533-553.

Pescatello, L. S. & Kulikowich, J. M. (2001). The aftereffects of dynamic exercise on ambulatory blood pressure. Med.Sci.Sports Exerc., 33, 1855-1861.

Rao, M. S. (2003). Pathogenesis and consequences of essential hypertension. J.Indian Med.Assoc., 101, 251-253.

Ray, C. A. & Carrasco, D. I. (2000). Isometric handgrip training reduces arterial pressure at rest without changes in sympathetic nerve activity. Am.J.Physiol Heart Circ.Physiol, 279, H245-H249.

Ray, C. A. & Hume, K. M. (1998). Sympathetic neural adaptations to exercise training in humans: insights from microneurography. Med.Sci.Sports Exerc., 30, 387-391.

Roltsch, M. H., Mendez, T., Wilund, K. R., & Hagberg, J. M. (2001). Acute resistive exercise does not affect ambulatory blood pressure in young men and women. Med.Sci.Sports Exerc., 33, 881-886.

Rowe, J. W. (1987). Clinical consequences of age-related impairments in vascular compliance. Am.J.Cardiol., 60, 68G-71G.

Safar, M. E., Laurent, S., Pannier, B. M., & London, G. M. (1987). Structural and functional modifications of peripheral large arteries in hypertensive patients. J.Clin.Hypertens., 3, 360-367.

Schmidt-Trucksass, A. S., Grathwohl, D., Frey, I., Schmid, A., Boragk, R., Upmeier, C., Keul, J., & Huonker, M. (1999). Relation of leisure-time physical activity to structural and functional arterial properties of the common carotid artery in male subjects. Atherosclerosis, 145, 107-114.

Seals, D. R. (2003). Habitual exercise and the age-associated decline in large artery compliance. Exerc.Sport Sci.Rev., 31, 68-72.

Seals, D. R., Washburn, R. A., Hanson, P. G., Painter, P. L., & Nagle, F. J. (1983). Increased cardiovascular response to static contraction of larger muscle groups. J.Appl.Physiol, 54, 434-437.

Sherman, D. L. (2000). Exercise and endothelial function. Coron.Artery Dis., 11, 117-122.

Silva, G. J., Brum, P. C., Negrao, C. E., & Krieger, E. M. (1997). Acute and chronic effects of exercise on baroreflexes in spontaneously hypertensive rats. Hypertension, 30, 714-719.

Sinoway, L., Shenberger, J., Leaman, G., Zelis, R., Gray, K., Baily, R., & Leuenberger, U. (1996). Forearm training attenuates sympathetic responses to prolonged rhythmic forearm exercise. J.Appl.Physiol, 81, 1778-1784.

Sinoway, L. I., Shenberger, J., Wilson, J., McLaughlin, D., Musch, T., & Zelis, R. (1987). A 30-day forearm work protocol increases maximal forearm blood flow. J.Appl.Physiol, 62, 1063-1067.

Smolander, J., Aminoff, T., Korhonen, I., Tervo, M., Shen, N., Korhonen, O., & Louhevaara, V. (1998). Heart rate and blood pressure responses to isometric exercise in young and older men. Eur.J.Appl.Physiol Occup.Physiol, 77, 439-444.

Somers, V. K., Conway, J., Johnston, J., & Sleight, P. (1991). Effects of endurance training on baroreflex sensitivity and blood pressure in borderline hypertension. Lancet, 337, 1363-1368.

Somers, V. K., Leo, K. C., Shields, R., Clary, M., & Mark, A. L. (1992). Forearm endurance training attenuates sympathetic nerve response to isometric handgrip in normal humans. J.Appl.Physiol, 72, 1039-1043.

Sun, D., Huang, A., Koller, A., & Kaley, G. (1998). Adaptation of flow-induced dilation of arterioles to daily exercise. Microvasc.Res., 56, 54-61.

Tanaka, H., DeSouza, C. A., & Seals, D. R. (1998). Absence of age-related increase in central arterial stiffness in physically active women. Arterioscler.Thromb.Vasc.Biol., 18, 127-132.

Tanaka, H., Dinenno, F. A., Monahan, K. D., Clevenger, C. M., DeSouza, C. A., & Seals, D. R. (2000). Aging, habitual exercise, and dynamic arterial compliance. Circulation, 102, 1270-1275.

Taylor, A. C., McCartney, N., Kamath, M. V., & Wiley, R. L. (2003). Isometric training lowers resting blood pressure and modulates autonomic control. Med.Sci.Sports Exerc., 35, 251-256.

Thomas, D. P., Zimmerman, S. D., Hansen, T. R., Martin, D. T., & McCormick, R. J. (2000). Collagen gene expression in rat left ventricle: interactive effect of age and exercise training. J.Appl.Physiol, 89, 1462-1468.

Tortora, G. & Garbowski, S. (1996). Principles of Anatomy and Physiology. Menlo Park, California: Addison Wesley Longman Inc.

Vaitkevicius, P. V., Fleg, J. L., Engel, J. H., O'Connor, F. C., Wright, J. G., Lakatta, L. E., Yin, F. C., & Lakatta, E. G. (1993). Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation, 88, 1456-1462.

Van Hoof, R., Macor, F., Lijnen, P., Staessen, J., Thijs, L., Vanhees, L., & Fagard, R. (1996). Effect of strength training on blood pressure measured in various conditions in sedentary men. Int.J.Sports Med., 17, 415-422.

Van Merode, T., Hick, P. J., Hoeks, A. P., Rahn, K. H., & Reneman, R. S. (1988). Carotid artery wall properties in normotensive and borderline hypertensive subjects of various ages. Ultrasound Med.Biol., 14, 563-569.

Vasan, R. S., Larson, M. G., Leip, E. P., Evans, J. C., O'Donnell, C. J., Kannel, W. B., & Levy, D. (2001). Impact of high-normal blood pressure on the risk of cardiovascular disease. N.Engl.J.Med., 345, 1291-1297.

Whelton, S. P., Chin, A., Xin, X., & He, J. (2002). Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann.Intern.Med., 136, 493-503.

Wiley, R. L., Dunn, C. L., Cox, R. H., Hueppchen, N. A., & Scott, M. S. (1992). Isometric exercise training lowers resting blood pressure. Med.Sci.Sports Exerc., 24, 749-754.

APPENDIX A

Pulse Pressure in the Carotid and Brachial Arteries: Within Investigator and Between Investigator Reproducibility

This appendix shows the between day and between investigator reproducibility of PP measures. On two separate days, 4 volunteers were tested at the same time of day. On each day, two investigators measured pulse pressure at the brachial and carotid arteries. Values were obtained using a combination of applanation tonomtery at the radial artery and applanation tonomety in either the brachial or carotid artery. The mean coefficient of variation (CV) between day 1 and day 2 was 14.7 % and 11.3% for the carotid and brachial arteries respectively. The mean CV between the two investigators was 9.3% and 6.6% for the carotid and brachial arteries respectively. This data indicates that PP measurements as obtained by applanation tonometry were reproducible across different test days and between different investigators.

INTRODUCTION

PP, the difference between SBP and DBP, is considered a valuable measure of CVD risk(Benetos et al., 1997b) while the contour and velocity of the pulse wave are indices of arterial stiffening(Izzo, Jr. et al., 2001). PP is also an integral component of the arterial distensibility equation.

Using brachial sphygmomanometry, arterial pressure can be described in terms of the two extremes between which it fluctuates (Kelly et al., 1989). Due to the increasing interest in the arterial stiffening that accompanies aging and hypertension, assessment of PP in central and peripheral arteries is gaining attention. To document PP in both central and peripheral arteries, an accurate noninvasive method was required. Based on the principle of applanation tonometry, a pencil type probe containing a micromanometer in its tip is held on the skin over the area of maximal arterial pulsation (Kelly et al., 1989). Previous research has found that pressure registered by the tonometer was not significantly different from an intra-arterially recorded wave (Armentano et al., 1995).

The purpose of this study was to determine the between day and between investigator reproducibility of PP in the carotid and brachial arteries as obtained with an applanation tonometry device.

METHODS

Four subjects (mean age=67.3 years, mean height= 68.3 cm, mean weight=176.8 lbs) volunteered for this study and were tested on two separate days. Subjects arrived for testing at the same time of day and were requested to refrain from eating for four hours before the test, refrain from caffeine for 12 hours before the test, and refrain from vigourous exercise 24 hours before the test.

On each testing day PP measures from carotid and brachial artery were taken in triplicate by two investigators. Values reported were the average of these three measures.

Assessment of Carotid Artery Pulse Pressure

Upon entering the lab for testing, subjects were outfitted with one sets of 3 electrocardiogram (ECG) electrodes in order to record a HR throughout the testing session. One electrode was placed inferiorly to the right clavicle, one was placed inferiorly to the left clavicle, and the final one was placed on the left side of the torso inferiorly to the nipple. The subsequent ECG signal from the electrodes was captured by the Cardiomatic (Model MSC 71233, Medical Systems Corp, USA). This signal was then sent through an analogue to digital converter (Powerlab 16sp, AD Instruments) which had a sampling rate of 100-200 Hz per second and recorded on Powerlab Chart 4 Software (AD Instruments). Data was stored on a personal computer (IBM Nevista x86 compatible processor, White Plains, USA) for future analysis.

Pulse pressure was measured in the right common carotid artery and the radial artery on a beat-by-beat basis. This non-invasive method of pressure wave measurement used is based on the principle of applanation tonometry. Upon locating the point of

maximal arterial pulsation in the common carotid artery, a pencil type probe containing a high fidelity strain-gauge transducer (model SPT-301, Millar Instruments Inc., Texas, USA) was held on the skin over the site of maximal pulsation. The pencil-like probe was then pressed down on the carotid artery against underlying rigid structures. Once regular and consistent waveforms were obtained for a few cardiac beats, the pressure waves were recorded. Simultaneously to pressure waveforms being obtained in the carotid artery, they were also obtained from the radial artery using automated applanation tonometry (model CBM-7000, Colin Medical Instruments, San Antonio, USA). The automated tonometer involves a sensor which was placed over the point of maximal pulsation in the radial artery and beat-by-beat blood pressure waveforms were obtained. The signal, or pressure waveforms, obtained from both the carotid and radial arteries were passed through an analogue to digital converter (Powerlab 16sp, AD Instruments, Colorado Springs, USA) with a sampling rate of 100-200 Hz per second. The resulting digital signal was recorded on Powerlab Chart 4 software (AD Instruements,Colorado Springs USA) and saved on a personal computer (IBM Nevista x86 compatible processor, White Plains, USA) for later analysis.

The pencil type probe used in assessing PP in the carotid artery provides and uncalibrated pressure waveform in volts which we converted to mmHg using the radial artery pressure as a reference. The pressure signal obtained by tonometry in the carotid was calibrated by assigning the DBP measured by radial tonometry to its minimum pressure value, and the MAP (1/3(SBP-DBP) + DBP) as assessed by radial tonometry to its average value. This procedure is based on the assumption that mean pressure does not

change in large conduit arteries and that diastolic pressure is not significantly different among carotid, brachial, and femoral arteries(Kelly et al., 1989). SBP however does not remain constant between central and peripheral arteries due to pulse wave amplification as the arterial pressure wave is transmitted down the arterial tree (Izzo, Jr. et al., 2001). Therefore, to determine SBP in the carotid artery, the DBP and MAP obtained by radial tonometry are equated with the corresponding signal in the carotid pressure waveform. The SBP in the carotid is then extrapolated from this relationship.

Assessment of Brachial Artery Pulse Pressure

Measurements of pulse pressure in the brachial artery were obtained in the same manner as in the carotid artery. The only difference was that the Millar pencil type probe was place over the point of maximal pulsation in the right brachial artery.

Analysis of the Coefficient of Variation

Essentially, two forms of variation were being measured in the present study. One investigator measured PP in the carotid and brachial arteries on day 1 and again on day 2. This will constitute the within investigator variability. Also on day 1, two separate investigators measured pulse pressure in the carotid and brachial arteries. This will be considered the between investigator variability. The mean and standard deviation were calculated for each subject and the CV was considered the standard deviation divided by the mean multiplied by 100. The CV was calculated for each subject comparing day 1 and day 2 in the within investigator reproducibility study. A CV was also calculated for the PP values obtain by investigator 1 and investigator 2 on day 1

which represents the between investigator reproducibility. The data are presented as the mean of these CV.

RESULTS

Results indicated that the within investigator reproducibility was 14.7% and 11.3% for the carotid and brachial arteries respectively (Fig 1).

Carotid Artery

T1	T2	mean	SD	CV	CV
59.67496	59.19562	59.43529	0.338947	0.005703	0.57028
40.10837	66.27534	53.19186	18.50284	0.347851	34.7851
59.66836	49.62471	54.64653	7.101928	0.129961	12.99612
40.66893	47.22592	43.94742	4.636489	0.105501	10.55008
					14.725

Brachial Artery

T1	T2	mean	SD	CV	CV
55.18372	66.92273	61.05322	8.300733	0.135959	13.5959
54.03344	64.95414	59.49379	7.722098	0.129797	12.97967
64.46445	54.49653	59.48049	7.048383	0.118499	11.84991
48.93883	53.92229	51.43056	3.523836	0.068516	6.851638
					11.319

Fig 1: Results from the within investigator reproducibility. PP values were taken by one investigator on two separate days.

The between investigator reproducibility was 9.3% and 6.6% for the carotid and brachial arteries respectively (Fig 2).

Carotid Artery

A	M	mean	SD	CV	CV
59.67496	50.48117	55.07807	6.500996	0.118032	11.80324
40.10837	34.29456	37.20147	4.110986	0.110506	11.0506
59.66836	58.12555	58.89695	1.090929	0.018523	1.852266
40.66893	48.64633	44.65763	5.64087	0.126314	12.63137
					9.33437

Brachial Artery

A	M	mean	SD	CV	CV
55.18372	56.08061	55.63216	0.634195	0.0114	1.13998
54.03344	49.61204	51.82274	3.126404	0.060329	6.032879
64.46445	54.98446	59.72445	6.703363	0.112238	11.22382
48.93883	43.51262	46.22572	3.836915	0.083004	8.300389
					6.674266

Fig 2: Results from the between investigator reproducibility study. PP measures were taken by two different investigators on the same day.

CONCLUSIONS

It has been demonstrated that PP measures made using applanation tonometry from the carotid and brachial arteries is a reproducible measure. Although the between investigator reproducibility is more impressive, one must consider that the measures were taken on the same day. Due to the increasing attention PP is receiving as both a CVD risk factor and an index of arterial stiffness, this non-invasive measurement tool will no doubt be used more frequently. Therefore, more studies are required to further characterize its reproducibility.

APPENDIX B

Study Data

Demographic Data

Subject #	Group	Age	Sex	Height (in)	Weight (lbs)	Medications	CVD
1	IHG	63	M	68	209	ACE, BB, CCB	YES
2	IHG	77	M	69	175	ACE, BB, Diuretic	YES
3	IHG	63	M	72	210	ACE, Diuretic	NO
4	IHG	67	F	60	187	CCB	NO
5	IHG	74	M	68	195	CCB, ACE	NO
6	IHG	68	M	64	160	CCB, ACE	NO
7	IHG	69	F	63	160	ACE, BB, Diuretic	YES
8	IHG	61	M	71	200	ACE	NO
9	IHG	57	M	68	150	ACE	NO
10	IHG	64	M	71	180	ACE	NO
	MEAN	**66.3**		**67.4**	**182.6**		
	SEM	**3.06**		**1.01**	**10.86**		
16	ILP	63	M	68	153	BB	YES
17	ILP	59	M	67	171	ACE, diuretic, BB, CCB	YES
18	ILP	64	M	69	199	ACE	NO
19	ILP	64	M	70.5	261	BB, ACE	YES
20	ILP	73	M	68	147	ACE	NO
21	ILP	56	M	73	223	ACE, BB	NO
22	ILP	22	M	72	185	ACE, diuretic, BB	NO
23	ILP	59	M	72	238	ACE, CCB	NO
24	ILP	58	M	69	255	ACE, BB	YES
	MEAN	**57.6**		**69.8**	**203.6**		
	SEM	**3.23**		**1.07**	**11.45**		
11	C	66	F	65	149	Diuretic	NO
12	C	68	F	65	211	ACE	YES
13	C	66	F	62	112	ACE	YES
14	C	64	M	70	194	ACE	NO
15	C	70	F	62	164	BB	YES
	MEAN	**66.8**		**64.8**	**166**		
	SEM	**4.33**		**1.43**	**15.36**		

Medication Abbreviations: BB - beta blocker, CCB - calcium channel blocker, ACE - ACE inhibitor

Systolic Blood Pressure (mmHg)

Subject #	Group	Pre	4wk	8wk
1	IHG	126.00	133.00	132.00
2	IHG	137.67	142.33	144.33
3	IHG	157.76	140.00	149.33
4	IHG	153.33	143.67	146.67
5	IHG	134.33	140.00	134.00
6	IHG	119.33	112.00	111.67
7	IHG	141.67	127.00	114.67
8	IHG	145.33	137.33	133.67
9	IHG	135.67	123.67	130.33
10	IHG	150.67	154.00	126.67
	MEAN	**140.18**	**135.30**	**132.33**
	SEM	**4.75**	**4.78**	**5.11**
16	ILP	143.67	139.67	129.67
17	ILP	124.00	153.00	131.00
18	ILP	108.18	119.00	118.33
19	ILP	149.67	146.67	164.33
20	ILP	143.67	140.67	148.33
21	ILP	125.67	125.67	136.00
22	ILP	98.00	100.67	104.00
23	ILP	144.33	156.67	161.00
24	ILP	154.33	152.33	135.67
	MEAN	**132.39**	**137.15**	**136.48**
	SEM	**5.01**	**5.04**	**5.39**
11	C	146.00	145.67	136.33
12	C	137.33	144.33	153.67
13	C	135.00	119.33	137.33
14	C	121.33	116.00	111.33
15	C	143.00	126.67	119.67
	Mean	**136.53**	**130.40**	**131.67**
	SEM	**6.72**	**6.76**	**7.23**

Diastolic Blood Pressure (mmHg)

Subject #	Group	Pre	4wk	8wk
1	IHG	69.33	75.67	79.67
2	IHG	64.67	66.33	68.33
3	IHG	84.21	82.00	79.33
4	IHG	83.33	87.67	81.67
5	IHG	69.97	88.67	81.67
6	IHG	74.67	71.67	73.00
7	IHG	65.67	62.67	55.67
8	IHG	92.00	85.33	84.00
9	IHG	83.33	70.33	76.67
10	IHG	97.33	85.00	84.00
	MEAN	**78.45**	**77.53**	**76.40**
	SEM	**3.53**	**3.04**	**3.62**
16	ILP	74.33	76.00	66.67
17	ILP	70.00	84.00	69.00
18	ILP	46.80	62.00	53.00
19	ILP	85.33	85.00	95.00
20	ILP	77.67	79.00	79.00
21	ILP	70.00	70.67	77.33
22	ILP	53.67	56.67	54.67
23	ILP	85.67	91.33	97.33
24	ILP	81.33	81.67	72.00
	MEAN	**71.64**	**76.26**	**73.78**
	SEM	**3.73**	**3.20**	**3.82**
11	C	69.00	69.50	59.67
12	C	67.00	68.67	73.33
13	C	67.00	57.00	66.00
14	C	72.33	68.67	69.67
15	C	69.00	61.33	59.33
	MEAN	**68.87**	**65.03**	**65.60**
	SEM	**5**	**4.3**	**5.13**

Carotid Artery Distensibility ($mmHg^{-1}$)

Subject #	Group	PRE	4wk	8wk
1	IHG	0.00124	0.00182	0.00163
2	IHG	0.00137	0.00113	0.00276
3	IHG	0.00116	0.00074	0.00138
4	IHG	0.00065	0.00181	0.00087
5	IHG	0.00108	0.00174	0.00114
6	IHG	0.00066	0.00091	0.00194
7	IHG	0.00106	0.00103	0.00120
8	IHG	0.00135	0.00118	0.00221
9	IHG	0.00136	0.00286	0.00238
10	IHG	0.00125	0.00137	0.00116
	MEAN	**0.00112**	**0.00146**	**0.00167**
	SEM	**0.0002**	**0.0002**	**0.0004**
16	ILP	0.00128	0.00223	0.00197
17	ILP	0.00176	0.00085	0.00779
18	ILP	0.00303	0.00117	0.00337
19	ILP	0.00073	0.00080	0.00198
20	ILP	0.00200	0.00147	0.00245
21	ILP	0.00260	0.00188	0.00229
22	ILP	0.00181	0.00390	0.00358
23	ILP	0.00118	0.00153	0.00133
24	ILP	0.00082	0.00107	0.00183
	MEAN	**0.00169**	**0.00166**	**0.00295**
	SEM	**0.0002**	**0.0002**	**0.0004**
11	C	0.00145	0.00126	0.00200
12	C	0.00084	0.00158	0.00084
13	C	0.00147	0.00177	0.00210
14	C	0.00172	0.00182	0.00145
15	C	0.00179	0.00186	0.00240
	MEAN	**0.00145**	**0.00166**	**0.00176**
	SEM	**0.00024**	**0.00032**	**0.00058**

Muscular Artery Distensibility: Exercising Limb ($mmHg^{-1}$)

Subject #	Group	PRE	4wk	8wk
1	IHG	0.0007	0.0009	0.0003
2	IHG	0.0008	0.0012	0.0005
3	IHG	0.0010	0.0004	0.0005
4	IHG	0.0008	0.0010	0.0008
5	IHG	0.0005	0.0005	0.0005
6	IHG	0.0008	0.0004	0.0016
7	IHG	0.0012	0.0023	0.0015
8	IHG	0.0004	0.0005	0.0008
9	IHG	0.0006	0.0011	0.0007
10	IHG	0.0006	0.0008	0.0006
	MEAN	**0.00073**	**0.00091**	**0.00079**
	SEM	**0.0002**	**0.0002**	**0.0004**
16	ILP	0.0018	0.0019	0.0013
17	ILP	0.0003	0.0004	0.0069
18	ILP	0.0033	0.0005	0.0009
19	ILP	0.0004	0.0007	0.0007
20	ILP	0.0016	0.0017	0.0011
21	ILP	0.0022	0.0005	0.0032
22	ILP	0.0016	0.0014	0.0017
23	ILP	0.0012	0.0007	0.0007
24	ILP	0.0004	0.0011	0.0008
	MEAN	**0.00142**	**0.00099**	**0.00192**
	SEM	**0.0002**	**0.0002**	**0.0004**
11	C	0.0005	0.0011	0.0014
12	C	0.0007	0.0026	0.0022
13	C	0.0014	0.0015	0.0009
14	C	0.0013	0.0012	0.0007
15	C	0.0007	0.0014	0.0005
	MEAN	**0.00094**	**0.00156**	**0.00113**
	SEM	**0.00029**	**0.00025**	**0.00058**

Muscular Artery Distensibility: Non Exercising Limb ($mmHg^{-1}$)

Subject #	Group	PRE	4wk	8wk
1	IHG	0.0004	0.0010	0.0006
2	IHG	0.0010	0.0009	0.0007
3	IHG	0.0006	0.0003	0.0007
4	IHG	0.0010	0.0006	0.0006
5	IHG	0.0004	0.0006	0.0011
6	IHG	0.0013	0.0018	0.0007
7	IHG	0.0008	0.0011	0.0012
8	IHG	0.0008	0.0007	0.0013
9	IHG	0.0006	0.0008	0.0012
10	IHG	0.0008	0.0010	0.0006
	MEAN	**0.0008**	**0.0009**	**0.0009**
	SEM	**0.0010**	**0.0001**	**0.0001**
16	ILP	0.0007	0.0013	0.0011
17	ILP	0.0006	0.0005	0.0006
18	ILP	0.0016	0.0007	0.0006
19	ILP	0.0010	0.0008	0.0007
20	ILP	0.0008	0.0009	0.0008
21	ILP	0.0011	0.0005	0.0007
22	ILP	0.0010	0.0021	0.0017
23	ILP	0.0007	0.0006	0.0003
24	ILP	0.0013	0.0007	0.0009
	MEAN	**0.00098**	**0.00089**	**0.00083**
	SEM	**0.0001**	**0.0002**	**0.0001**
11	C	0.0004	0.0006	0.0006
12	C	0.0006	0.0019	0.0014
13	C	0.0014	0.0009	0.0007
14	C	0.0004	0.0006	0.0011
15	C	0.0007	0.0012	0.0007
	MEAN	**0.00069**	**0.00103**	**0.00091**
	SEM	**0.00014**	**0.00020**	**0.00015**

APPENDIX C

ANOVA and Post Hoc Summary Tables

DEMOGRAPHIC STATISTICAL SUMMARY

AGE, HEIGHT, WEIGHT

1 – Factor (Group) ANOVA on Demographic Variables

Dep. Variable	df effect	MS effect	df error	MS error	F-ratio	p-level
AGE	2	223.75	21	93.77	2.3862	0.116457
HEIGHT	2	41.89	21	10.25	4.088	0.031656*
WEIGHT	2	2432.7	21	1180.0	2.0615	0.152242

* GROUP means are significantly different ($p<0.05$)

Tukey's HSD
Probabilities for Post Hoc Tests
Main Effect: GROUP

		{1}	{2}	{3}
		67.4	69.833	64.8
IHG	{1}		0.245998	0.319110
ILP	{2}	0.245998		0.026771*
C	{3}	0.319110	0.026771*	

* GROUP means are significantly different ($p<0.05$)

SYSTOLIC BLOOD PRESSURE

Summary of all Effects

1-GROUP, 2-TIME
Mixed 2-Way ANOVA

Effect	df Effect	MS effect	df Error	MS error	F-ratio	p-level
1	2	49	21	585	0.083	0.920541
2	2	48	42	65	0.736	0.485021
12	4	112	42	65	1.706	0.166679

DIASTOLIC BLOOD PRESSURE

Summary of all Effects

1-GROUP, 2-TIME
Mixed 2-Way ANOVA

Effects	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
1	2	600.8	21	295.2	2.036	0.155588
2	2	7.9	42	27.2	0.290	0.749536
12	4	35	42	27.2	1.288	0.289962

CAROTID ARTERY DISTENSIBILITY

Summary of All Effects

1-GROUP, 2-TIME
Mixed 2-Way ANOVA

Effect	df Effect	MS Effect	df Error	MS error	F-ratio	p-level
1	2	0.000003	21	0.000001	3.4421	0.050938*
2	2	0.000003	42	0.000001	3.9068	0.027794*
12	4	0.000001	42	0.000001	1.2807	0.292834

* Main effect of GROUP ($p<0.05$)
* Main effect of TIME ($p<0.05$)

Tukey's HSD
Probabilities for Post Hoc Tests
Main Effect: GROUP

		{1} **0.00141**	{2} **0.00210**	{3} **0.00162**
IHG	{1}		0.043224*	0.789867
ILP	{2}	0.043224*		0.316277
C	{3}	0.789867	0.316277	

* GROUP means are significantly different ($p<0.05$)

Tukey's HSD
Probabilities for Post Hoc Tests
Main Effect: TIME

		{1} **0.00140**	{2} **0.00157**	{3} **0.00217**
Pre	{1}		0.776611	0.011110*
4 week	{2}	0.776611		0.058130
8 week	{3}	0.011110*	0.058130	

* TIME means are significantly different ($p<0.05$)

MUSCULAR ARTERY DISTENSIBILITY
EXERCISING LIMB

Summary of All Effects

1-GROUP, 2-TIME
Mixed 2-Way ANOVA

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
1	2	0.000003	21	0.000001	4.3909	0.025516*
2	2	0.000000	42	0.000001	0.3841	0.683458
12	4	0.000001	42	0.000001	1.1811	0.333009

*Main effect of GROUP ($p<0.05$)

Tukey's HSD
Probabilities for Post Hoc Tests
Main Effect: GROUP

		{1} **0.0081**	{2} **0.00144**	{3} **0.00121**
IHG	{1}		0.020908*	0.286214
ILP	{2}	0.020908*		0.653982
C	{3}	0.286214	0.653982	

*GROUP means are significantly different ($p<0.05$)

MUSCULAR ARTERY DISTENSIBILITY
NON EXERCISING LIMB

Summary of All Effects

1-GROUP, 2-TIME
Mixed 2-Way ANOVA

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
1	2	0.000000	21	0.000000	0.1397	0.870382
2	2	0.000000	42	0.000000	0.6651	0.519561
12	4	0.000000	42	0.000000	0.8747	0.487174