ISOMETRIC TRAINING IN MEDICATED HYPERTENSIVE INDIVIDUALS

EFFECTS OF ISOMETRIC HANDGRIP TRAINING ON RESTING ARTERIAL BLOOD PRESSURE AND ARTERIAL COMPLIANCE IN MEDICATED HYPERTENSIVE INDIVIDUALS

By

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A Thesis

Submitted to the School of Graduate Studies

In Partial Fulfillment of the Requirements

For the Degree

Master of Science

McMaster University

MASTER OF SCIENCE (2004) McMaster University

(Human Biodynamics) Hamilton, Ontario

TITLE	Effects of Isometric Handgrip Training on Resting Arterial Pressure and Arterial Compliance in Medicated Hypertensive Individuals
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NUMBER OF PAGES:	117, xii

ABSTRACT

This study examined the effects of isometric handgrip training (IHG) on resting blood pressure and resting arterial compliance in the carotid and brachial arteries of medicated hypertensive individuals. Previous studies found that isometric training reduced resting arterial blood pressure (RBP) in high-normal and medicated hypertensive individuals. Investigators have also found an improvement in central arterial compliance with aerobic training and a reduction in central arterial compliance with age, cardiovascular disease and resistance training. The effects of isometric training on arterial compliance have not been examined previously.

Ten participants participated in a one-hand IHG intervention, nine participants in a two-hand IHG intervention and 5 participants served as the non-exercising controls. Each experimental group performed four, 30% maximal voluntary IHG contractions for 2 minutes, 3 days a week, for 8 weeks. The one-hand group trained only their non-dominant hand, while the two-hand group trained both hands. Measurements of resting arterial blood pressure, and cross sectional compliance of the brachial and carotid arteries were made pre-training, after four weeks of training and after the completion of the eight-week training protocol.

There were no changes in resting arterial blood pressure after training. Mean carotid and brachial artery diameters did not change with resistance training. There were no significant changes in brachial or carotid cross sectional compliance with isometric training. In conclusion, moderated level isometric training did not elicit changes in

resting arterial blood pressure and resting muscular and elastic arterial compliance in medicated hypertensive individuals compared to a non-exercising control group.

ACKNOWLEDGEMENTS

I would like to thank the many people who have supported me throughout this amazing journey. To Dr. Neil McCartney and Dr. Maureen MacDonald, for providing me the opportunity to complete my degree with continual encouragement and guidance. Your patience and trust in my ability was truly appreciated.

I would like to thank my co-investigators Cheri, Adrienne, Mark and Robyn for making our yearlong experiment enjoyable and informative. You were always there to answer my questions and keep our experiences fun and memorable.

To the MacTurltles and MacSeniors; thank you for your participation in my project. Without your enthusiasm and motivation this project would not have been possible. Thank you to my friend Karen Winegard. Your support and assistance throughout the project was truly appreciated.

I would like to thank my family who have always encouraged, loved and believed in me, regardless of the task. Finally I would like to thank my patient and understanding husband, Matt, who's support was unwavering. No matter how busy or tough times were, you were my rock – thank you!

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LIST OF ABBREVIATIONS

1HG	One hand isometric handgrip training
2HG	Two hand isometric handgrip training
ABP	Arterial blood pressure
MAP	Mean arterial pressure
PP	Pulse pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
Q	Cardiac output
TPR	Total peripheral resistance
HR	Heart rate
SV	Stroke volume
CNS	Central nervous system
SNS	Sympathetic nervous system
NE	Norepinephrine
RAAS	Renin-angiotensin-aldosterone system
ADH	Antidiuretic hormone
ACE	Angiotensin converting enzyme
ANP	Atrial natriuretic peptide
NO	Nitric oxide
CHD	Coronary heart disease
PVD	Peripheral vascular disease
CWT	Circuit weight training
MSNA	Muscle sympathetic nerve activity
LDL	Low density lipoprotein
HDL	High density lipoprotein
MVC	Maximal voluntary contractions
ECG	Electrocardiogram
AMS	Arterial measurement system
HSD	Tukeys honestly significant difference
CSC	Cross sectional compliance

1.1 Introduction

Aerobic exercise training has been acknowledged as an important non-pharmacological method of treatment for individuals with hypertension (Hagberg, Park, & Brown, 2000). Until recently isometric exercise training was disregarded as a potential therapy for hypertension due to potential effects of the large pressor response associated with static contractions. Several investigators have examined the physiological responses to intermittent, moderate levels of isometric training (Ray & Carrasco, 2000; Sinoway, Shenberger, Wilson et al., 1987; Somers, Leo, Shields et al., 1992; Taylor, McCartney, Kamath et al., 2003; Wiley, Dunn, Cox et al., 1992), and found a reduced pressor response compared to sustained contraction protocols. The reduced acute pressor response is an important component for examination of the beneficial long-term effects of moderate levels of isometric training. In an early investigation, Kivelhoff and Huber (1971) found that brief whole body isometric exercise could elicit a hypotensive effect over several weeks of training. Buck and Donner (1985) confirmed these results by comparing the amount of isometric effort in various jobs to the incidence of hypertension, concluding that hypertension was prevented with isometric exercise. More recently Wiley and colleagues (1992) and Taylor and colleagues (2003) found that controlled studies of moderate levels of isometric handgrip exercise could elicit reductions in resting blood pressure in individuals with high normal blood pressure and hypertension.

Even a moderate elevation in resting blood pressure can shorten a person's life expectancy (Mensah, 2002), but this risk can be reduced by effective control of systolic and diastolic blood pressure (Mensah, 2002). Pharmacological therapy is most often

the treatment of choice, but due to numerous side effects and reduced compliance with the regimen, alternative non-drug therapies are being examined. Approximately 75% of hypertensive individuals who exercise will benefit from a reduction in arterial blood pressure (Hagberg, Park, & Brown, 2000). Aerobic exercise is considered the most effective mode of exercise in the prevention and treatment of hypertension (Nicholls, 1990; Wallace, 2003). Resistance training has also been suggested to elicit an anti-hypertensive effect by some investigators (Blumenthal, Siegel, & Appelbaum, 1991; Harris & Holly, 1987; Hurley, Hagberg, Goldberg et al., 1988), but not by others (Cononie, Graves, Pollock et al., 1991). Limited investigations have examined the effects of isometric training on resting blood pressure (Ray & Carrasco, 2000; Taylor, McCartney, Kamath et al., 2003; Wiley, Dunn, Cox et al., 1992), however the results have all indicated the potential for hypotensive effects.

The exact mechanisms responsible for the reductions in resting blood pressure with exercise are unknown, and are likely a complex combination of metabolic, cardiovascular and neural factors (Pagani, Somers, Furlan et al., 1988). Several mechanisms have been proposed including changes in sympathetic nervous system activity (Pagani, Somers, Furlan et al., 1988; Seals & Hagberg, 1984), genetics, improved endothelial functioning (Kokkinos, Narayan, & Papademetriou, 2001), reduced plasma norepinephrine levels (Kokkinos, Narayan, & Papademetriou, 2001) and/or changes in arterial structure (Tanaka, Reiling, & Seals, 1998). Arterial compliance, the ability of an artery to expand in response to an increase in pressure, has been associated with hypertension through observations of elevated pulse pressure in hypertensive individuals (Asmar, Rudnichi,

Blacher et al., 2001). Therefore an improvement in resting arterial blood pressure with isometric exercise could be a result of improved arterial compliance.

Reduced arterial compliance has a number of adverse effects including elevations in systolic blood pressure and pulse pressure, increased left ventricular tension (Miyachi, Donato, Yamamoto et al., 2003), less inhibition of sympathetic outflow and less increase in vagal tone resulting in greater blood pressure variability (Joyner, 2000). A variety of changes in arterial structure and mechanics contribute to reduced arterial compliance, however the exact mechanisms are still incompletely understood. Central elastic arterial compliance can be improved with common antihypertensive medications including calcium channel blockers, ACE inhibitors, nitrates and/or angiotensin II antagonists (Resnick & Lester, 2002). Regular aerobic exercise has recently been linked to improvements in age-associated reductions in large artery compliance in middle-aged and older adults (Ferreira, Twisk, Stehouwer et al., 2003; Tanaka, Dinenno, Monahan et al., 2000). Regular resistance training appears to reduce central elastic arterial compliance, however the studies were cross-sectional investigations. There are currently no data examining the effects of isometric training on elastic or muscular arterial compliance in healthy or hypertensive individuals. Therefore the current study was designed to examine the effects of isometric handgrip training on resting arterial blood pressure and resting arterial compliance in medicated hypertensive individuals.

Summary and Hypothesis

Current data suggest that isometric training is effective at lowering resting arterial blood pressure in hypertensive individuals, however the data are limited. The

mechanisms associated with a reduction in resting blood pressure are unknown and the effects of isometric training on arterial compliance and its association with reduced blood pressure have not been examined. Because it seems possible that the isometric handgrip exercises may have only a local effect on resting arterial compliance, a one-hand protocol (with equivalent work demands) was designed to assess whether or not any changes might be confined to the exercising arm alone or may also be measured in the control arm (indicating a systemic effect). Therefore, the purpose of this study was to 1) determine if one-hand isometric exercise elicits similar resting blood pressure reductions and increases in vascular compliance as two-handed isometric exercise in medicated hypertensive individuals and 2) to determine if isometric handgrip exercise will alter vascular compliance in the conduit artery directly supplying the exercising arm and/or the non-exercising muscular and elastic arteries in medicated hypertensive individuals. Subjects were randomized to a one-hand isometric training group (1HG) (n=10), two-hand isometric training group (2HG)(n=9) and a control group (n=6).

We hypothesized that 1) Eight weeks of one-hand and two-hand isometric handgrip exercise will result in similar resting blood pressure reductions versus controls in medicated hypertensives 2) one-hand isometric handgrip exercise training will result in similar increases in brachial artery compliance of the exercising arm as in the two-hand isometric handgrip exercise vs. controls 3) one-hand isometric exercise will result in similar increases in systemic elastic artery compliance as two-hand isometric exercise versus controls 4) one-hand isometric handgrip exercise will result in increased compliance in the brachial artery of the non-exercising arm versus control.

Chapter 2 Review of Literature

2.1 Introduction

In this review of literature, the topics covered include arterial blood pressure (ABP) measurement, and regulation, hypertension and its relationship with ageing, the pathophysiology of hypertension and the inter-relationships among arterial compliance, ageing and hypertension. The purpose of this review is to examine and understand the effects that isometric training may have on resting arterial blood pressure and resting arterial compliance in hypertensive individuals.

Hypertension is a complicated and prevalent disease that affects more than 50 million people in the United States alone (Joint National Committee, 1997). Elevated resting blood pressure is a major cardiovascular risk factor (Martel, Hurlbut, Lott et al., 1999) associated with high morbidity and mortality, so early detection and treatment are very important (Cohn, 1999). Unfortunately, high blood pressure is inadequately treated in approximately 73 percent of hypertensives, most likely due to the asymptomatic nature of the disease and non-compliance with recommended therapies (Joint National Committee, 1997).

2.2 Arterial Blood Pressure

The regulation of arterial blood pressure is a primary factor in the examination of hypertension. Blood pressure is the force exerted by the blood against any unit area of the vessel wall (Guyton & Hall, 1996). Increases in arterial blood pressure (ABP) promote blood flow from areas of high to low pressure and allow perfusion to diverse parts of the body (Brubaker, Kaminsky, & Whaley, 2002; Guyton & Hall, 1996).

Indexes of ABP include systolic, diastolic, mean arterial and pulse pressure. The principal components of arterial blood pressure include a steady component (MAP) and a pulsatile component (PP) (Franklin, Khan, Wong et al., 1999). Systolic blood pressure (SBP) is the pressure in the arteries during the contractile phase of the heart (Brubaker, Kaminsky, & Whaley, 2002). The pressure remaining in the arteries during the relaxation phase between contractions is classified as diastolic blood pressure (DBP). Mean arterial pressure (MAP) is not an average pressure of SBP and DBP, but is a time-weighted sum of SBP and DBP that can be calculated in a variety of ways. MAP is considered the steady component of arterial BP because it remains almost constant along the whole arterial tree (Safar & Laurent, 2003). Pulse pressure (PP) is the difference between SBP and DBP. Arterial blood pressure is a homeostatic index, which varies continually, and a complex system of mechanisms work to adjust and respond appropriately to changes in blood pressure within a specific range.

2.2.1 Measurement of Arterial Blood Pressure

In the research environment, the reliability and accuracy of invasive continuous blood pressure measurements is preferred over non-invasive methods because of the superior reliability and accuracy (Drzewiecki, Melbin, & Noordergraaf, 1983). Invasive, direct methods utilizing an intra-arterial catheter are the gold standard for blood pressure measurements, but investigators more often record blood pressure with the less expensive and less time-consuming, non-invasive methods. A problem with direct intra-arterial measurement is that often only one ABP recording is taken (e.g. for baseline ABP) resulting in less accurate ABP values than several indirect measurements taken over a

period of time. Indirect, non-invasive methods include manual oscillometric, automatic oscillometric and arterial tonometry techniques. Manual and automatic oscillometric techniques utilize an inflatable cuff wrapped around an extremity to collapse large blood vessels and occlude blood flow. A stethoscope is used with the manual oscillometric technique to hear the lumen opening as the pressure in the cuff is released (SBP) and when blood turbulence ceases (DBP). A pressure sensor is used with the automatic oscillometric technique to document blood pressure values. The size of the cuff in oscillometric blood pressure measurements is critical for adequate cuff pressure transmission and accurate readings (Drzewiecki, Melbin, & Noordergraaf, 1983). The manual oscillometric method relies on the hearing of the investigator to determine the maximum and minimum blood pressure values. Therefore, the investigator may not hear the actual blood pressure values accurately. A limitation with both oscillometric blood pressure techniques is that only periodic blood pressure values can be recorded due to the obstruction of blood flow. Arterial tonometry addresses this concern by recording continuous pressure signals throughout the cardiac cycle. This non-invasive method is based on the theory of flattening the arterial wall with a probe to allow for pressure measurements that are equivalent to true intra-arterial pressures (Kelly, Hayward, Avolio et al., 1989). Too little or too much flattening of the arterial wall can distort the pressure signal; therefore, it is important that the investigator be properly trained. Land marking is also important to ensure recordings occur in the same area of the artery in repeated testing sessions.

2.2.2 Physiology of Normal ABP Control

Mean arterial blood pressure is controlled by two important physiological factors: cardiac output (Q), the amount of blood ejected by a single ventricle in one minute, and the total peripheral resistance (TPR) to the flow of blood. Cardiac output is a product of heart rate (HR) and stroke volume (SV); therefore, adjusting SV by increasing/decreasing the amount of blood ejected and/or heart rate can influence the MAP. The force of ventricular contraction, filling pressure and afterload determines stroke volume, while heart rate is governed by sympathetic and parasympathetic stimulation (Bakris & Mensah, 2002). MAP is also influenced by an alteration in TPR through vasodilation or vasoconstriction of the systemic vasculature. All of the above-mentioned factors that influence arterial blood pressure are regulated by a combination of short-term, intermediate and slower-acting mechanisms that maintain arterial blood pressure within narrow limits.

2.2.3 Mechanisms of ABP Regulation

The complex systems that influence and maintain ABP can be characterized by the amount of time required for them to be activated. The following mechanisms control ABP by altering peripheral resistance, stroke volume and/or heart rate (Guyton & Hall, 1996; Seeley, Stephens, & Tate, 2003). Short-term mechanisms react within seconds or minutes of a change in blood pressure, intermediate mechanisms respond within minutes or hours and late-acting mechanisms regulate ABP over days, months and years (Guyton & Hall, 1996).

Short-term mechanisms respond quickly (beat-to-beat), but once ABP is altered for a few hours to days, primary control of ABP occurs by slower-acting mechanisms (Seeley, Stephens, & Tate, 2003). The baroreceptor system, chemoreceptors, the central nervous system (CNS) ischemic response, and the adrenal medullary mechanism are classified as short-term mechanisms and act primarily through the autonomic nervous system to regulate acute changes in blood pressure (Krakoff, Dziedzic, Mann et al., 1985).

The baroreceptor system provides rapid BP regulation within a very narrow range (Seeley, Stephens, & Tate, 2003). This allows for rapid responses to and detection of small alterations in ABP. The arterial baroreceptors are located in the systemic circulation in the internal carotid arteries and the wall of the aortic arch. Pressures from 60 to 180 mmHg stimulate the baroreceptors in the internal carotid arteries, while the receptors in the wall of the aortic arch are stimulated approximately 30 mmHg higher (Guyton & Hall, 1996). Aortic baroreceptor reflex accounts for two-thirds and the carotid receptors one-third of the complete arterial reflex response (Ferguson, Abboud and Mark, 1985; Shi et. al, 1995). An increase in ABP results in stretching of the arteries that activates the baroreceptors to send inhibitory signals to the vasomotor center to reduce arterial pressure (Bakris & Mensah, 2002). These stretch receptors respond to an acute increase in ABP by signalling for a reduction in sympathetic nervous system (SNS) activity to the arterioles to reduce TPR and cardiac filling pressure (Bakris & Mensah, 2002). Activation of arterial baroreceptors also results in excitation of the vagus nerve, thereby reducing heart rate and myocardial contractility (Bakris & Mensah, 2002). The

baroreceptors also have the ability to increase ABP when a drop in ABP occurs (i.e. after standing rapidly from a sitting position). The buffering capacity of the arterial baroreceptors ensures the adjustment in ABP is appropriate (Brubaker, Kaminsky, & Whaley, 2002) and after 1-3 days the arterial baroreceptors will adjust to the new sustained ABP (Shi et al, 1995).

The chemoreceptor reflex operates similarly to the baroreceptor reflex except that instead of stretch receptors, chemosensitive cells activate a response (Guyton & Hall, 1996). Chemoreceptors are chemosensitive cells located in the carotid and aortic bodies where they monitor the changes in plasma oxygen, carbon dioxide and hydrogen levels (Bakris & Mensah, 2002; Seeley, Stephens, & Tate, 2003). This mechanism functions primarily in emergency situations at very low pressures (<80mmHg) by stimulating the vasomotor center to elevate MAP and increase blood flow to the brain and heart when oxygen levels fall (Guyton & Hall, 1996; Seeley, Stephens, & Tate, 2003).

The CNS ischemic response is also activated by a significant reduction in ABP levels (i.e. <50mmHg) in emergency situations (Guyton & Hall, 1996; Seeley, Stephens, & Tate, 2003). This mechanism is activated by reduced cerebral blood flow to the medulla oblongata, low plasma oxygen, increased carbon dioxide levels and reduced pH levels. Activation of the CNS ischemic response results in increased ABP through stimulation of the vasomotor center (Guyton & Hall, 1996; Seeley, Stephens, & Tate, 2003). The CNS ischemic response is one of the most powerful activators of sympathetic vasoconstriction as it can elevate mean arterial pressure to levels as high as 250 mmHg and totally occlude some peripheral vessels (Guyton & Hall, 1996).

Stimulation of the adrenal medulla by the SNS in response to an increase in physical activity, stress or a reduction in blood pressure results in the release of norepinephrine (NE) and epinephrine (Guyton & Hall, 1996; Seeley, Stephens, & Tate, 2003). Epinephrine magnifies neural vasoconstriction through the smooth muscle alpha-receptors, resulting in increased TPR and therefore ABP, as well as dilating the coronary arteries by stimulation of the beta-receptors to promote an increase in blood flow to the cardiac muscle (Brubaker, Kaminsky, & Whaley, 2002; Seeley, Stephens, & Tate, 2003). Norepinephrine released by the adrenal medulla and nerve endings increases HR, SV and vasoconstriction of blood flow to the skin in an attempt to increase ABP (Seeley, Stephens, & Tate, 2003).

Intermediate acting mechanisms become active within 30 minutes to several hours and include the renin-angiotensin-aldosterone (RAAS) system, antidiuretic hormone (ADH), atrial natriuretic, stress-relaxation of the vasculature and fluid shift from the circulation through the capillary walls (Bakris & Mensah, 2002; Guyton & Hall, 1996).

A drop in blood pressure sensed by the baroreceptors stimulates the release of renin from the kidneys (Bakris & Mensah, 2002; Guyton & Hall, 1996). Renin converts angiotensinogen, released from the liver, to angiotensin I. Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II in the small blood vessels of the lungs. Angiotensin II acts to increase ABP to desired levels by increasing TPR via vasoconstriction of the arterioles, indirect water and sodium retention through stimulation of the release of aldosterone and by directly increasing the absorption of sodium (Bakris

& Mensah, 2002; Brubaker, Kaminsky, & Whaley, 2002; Guyton & Hall, 1996; Seeley, Stephens, & Tate, 2003).

Antidiuretic hormone (ADH) is released from the posterior pituitary gland primarily in response to reduction in inhibitory tone by the baroreceptor signal of an acute, substantial decrease in BP (Bakris & Mensah, 2002; Brubaker, Kaminsky, & Whaley, 2002; Guyton & Hall, 1996; Seeley, Stephens, & Tate, 2003). ADH acts to reduce the amount of urine production resulting in water conservation and assists in returning BP to normal levels (Seeley, Stephens, & Tate, 2003).

The cells of the atria are stimulated to release the hormone, atrial natriuretic peptide (ANP) when stretched (Bakris & Mensah, 2002; Brubaker, Kaminsky, & Whaley, 2002). ANP acts to reduce venous return in the kidneys by decreasing blood volume through an increase in urine production (Seeley, Stephens, & Tate, 2003). Reduced peripheral vascular resistance also occurs due to the dilation of the arteries and veins by ANP (Lang, Unger & Ganton, 1987; Rubattu & Volpe, 2001).

The fluid shift response acts within minutes of a shift in blood pressure, however it can take hours to reach its maximal effect (Seeley, Stephens, & Tate, 2003). The shift occurs in response to small alterations in pressure across capillary walls to store fluid in the interstitial space during elevated ABPs and move fluid into the capillaries when ABP is reduced (Bakris & Mensah, 2002; Brubaker, Kaminsky, & Whaley, 2002; Seeley, Stephens, & Tate, 2003).

Slower acting mechanisms are very important because of their ability to efficiently regulate ABP over days to years (Guyton, 1990). The kidney is one system

responsible for the long-term blood pressure and volume control. The kidneys respond to alterations in ABP levels by regulating salt and water excretion (Bakris & Mensah, 2002). Increases in extracellular fluid will result in increased blood volume, venous return, cardiac output and arterial pressure (Guyton & Hall, 1996). When the shift is sensed by the sensory mechanisms, the kidneys can adjust to excrete larger amounts of fluid to reduce ABP to appropriate levels for the individual.

Normal ABP control allows for significant flexibility in the ABP set point (Bakris & Mensah, 2002). The short, intermediate and long-term mechanisms listed above allow ABP to adjust to meet the body's physiologic demands, and return BP to the resting set point for that individual after the demands are completed. In hypertension a number of regulatory control mechanisms are impaired resulting in an abnormal pattern of ABP regulation.

2.3 Hypertension

Even a moderate elevation in blood pressure will shorten a person's life expectancy (Mensah, 2002). The optimal blood pressure for a healthy adult is considered to be less than 120/80 mmHg at rest (Joint National Committee, 1997). Although there is no clear threshold for the diagnosis of hypertension, the risk of coronary heart disease events continuously increase with increasing SBP starting as low as 120 mmHg (Martel, Hurlbut, Lott et al., 1999). The 6th Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (1997), has examined data from the Framingham Heart Study and other epidemiological studies to define hypertension according to the following guidelines; Stage one mild hypertension (140-159/90-99

mmHg); Stage two for moderate hypertension (160-179/100-109 mmHg); Stage three severe hypertension (180/110 mmHg). Isolated systolic hypertension was defined as systolic blood pressure 140 mmHg and diastolic blood pressure less than 90 mmHg (Joint National Committee, 1997). It is recommended that the diagnosis of hypertension should be preceded by at least 3 sets of blood pressure measurements over a span of at least 3 months (Kaplan, 2001). Current guidelines for the diagnosis and management of hypertension have defined cardiovascular risk as an increase in SBP and/or an increase in DBP (Joint National Committee, 1997). Recent investigations have also found that elevations in PP were superior to increased SBP and/or DBP in predicting coronary heart disease risk in normotensive, treated and untreated hypertensive middle-aged and elderly individuals (Asmar, Rudnichi, Blacher et al., 2001; Franklin, Khan, Wong et al., 1999). Pulse pressure depends mainly on the stiffness of large arteries (Benetos, Laurent, Asmar et al., 1997a). In younger individuals there is a proportional increase in SBP and DBP due to vascular resistance (Franklin, Khan, Wong et al., 1999). The loss of elasticity in the aorta and major arterial conduits associated with aging consequently results in an disproportionate increase in SBP over DBP in middle-aged and elderly individuals (Dart & Kingwell, 2001). As large arteries stiffen with age, SBP rises and DBP falls resulting in an increased PP. Therefore, brachial artery cuff measurement of PP in the elderly as opposed to in the young becomes a more accurate indicator of central PP and improved predictor of CHD risk over SBP and DBP (Franklin, Khan, Wong et al., 1999).

Hypertension can be classified into one of four categories according to the origin of the disease. Secondary hypertension is diagnosed when a patient suffers from elevated

blood pressure due to a secondary process/disease that could be resolved with surgery or medication (Kaplan, 2001). Labile hypertension occurs when a patient with normal TPR suffers from an elevated blood pressure due to a hyperkinetic circulation associated with elevated resting heart rate and cardiac output (Sannerstedt, Julius, & Conway, 1970). In labile hypertension increased sympathetic and/or reduced parasympathetic nervous system activity are believed to induce the hyperkinetic circulation (Sannerstedt, Julius, & Conway, 1970). Patients whose ABP is raised at some times and normal at others are said to have labile hypertension (Bailey, 1980). However more recently, investigators have moved away from the term labile hypertension and have been focusing on the definition of borderline hypertension. Patients whose initial DBP reading is greater than 90mmHg and subsequent repeat readings are well below this value are advised that their ABP level is borderline and should be checked annually (Kaplan, 2001). Systolic hypertension involves a disproportionate increase in SBP over a normal or low DBP (Safar & Laurent, 2003). More than 90% of all hypertensive persons suffer from primary hypertension, a disease with no recognizable origin (Guyton & Hall, 1996; Harris & Holly, 1987; Kaplan, 2001). This is the type of hypertension that will be discussed throughout the rest of this review.

2.3.1 Aging and hypertension

Primary hypertension is uncommon in young adults, but the prevalence increases with age (Bakris & Mensah, 2002) . At age 65 the prevalence is 65% and at age 75, the prevalence is 75% (Bakris & Mensah, 2002). Hypertension in the elderly presents often as isolated systolic hypertension with normal or low DBP and systolic-diastolic

hypertension with a disproportionate increase of SBP over DBP (Safar & Laurent, 2003). The majority of older adults with primary hypertension are classified as having stage 1 or 2 hypertension (Joint National Committee, 1997). Increases in blood pressure make the largest relative risk factor contribution to cardiovascular mortality and morbidity among older adults (Taylor, Cornoni-Huntley, Curb et al., 1991).

As humans age, functional capacity is reduced and cardiovascular and metabolic systems begin to deteriorate (Fleg & Lakatta, 1988). Structural changes in the resistance vasculature resulting in increased total peripheral resistance, are considered an important factor in the development and maintenance of high blood pressure in both hypertension and with aging (James, Watt, Potter et al., 1995). Reversal of these structural modifications leading to a reduction in blood pressure has been identified as a clinically relevant and desirable goal in the treatment of hypertension in older adults (James, Watt, Potter et al., 1995).

Treatment of hypertension in the elderly has been shown to be effective in preventing major cardiovascular events in older hypertensive individuals (Cononie, Graves, Pollock et al., 1991; Martel, Hurlbut, Lott et al., 1999; Weber, 1995). Even older adults with normal to moderate elevations in ABP can lower their ABP with endurance exercise (Cononie, Graves, Pollock et al., 1991) and resistance exercise (Martel, Hurlbut, Lott et al., 1999). Tanaka and colleagues (1998) have shown that regular aerobic exercise reduces blood pressure in older men and women with stage 1 or 2 primary hypertension mediated possibly in part by changes in arterial structure, due to increased blood flow and arterial diameter or humoral changes.

2.3.2 Mechanisms of Primary Hypertension

In hypertension, alterations to both cardiac and arterial systems can occur. (Segers, Stergiopulos, & Westerhof, 2000). Arterial blood pressure is a product of cardiac output (Q) and total peripheral resistance (TPR) (Seals & Hagberg, 1984) and hypertension occurs as a result of an increase in TPR and/or Q. Primary hypertension is often characterized by an increase in TPR by 40-60% with normal Q (Cohn, 1999; Sannerstedt, Julius, & Conway, 1970).Increases in TPR in primary hypertension are associated with progressive increases in vascular resistance and subsequent cardiac and systemic vascular adaptations (Safar & Laurent, 2003).

Primary hypertension is associated with increased TPR, improper neurohumoral activation and impaired kidney function (Bakris & Mensah, 2002). Part of the difficulty in determining the factors causing hypertension is the slow and gradual development of the hypertension disease process. Genetic alterations (Bakris & Mensah, 2002; Hagberg, Park, & Brown, 2000; Weber, 1995), low birth weight because of fetal undernutrition (Irving, Shore, Belton et al., 2004; Lackland, Egan, & Ferguson, 2003; Law & Shiell, 1996), renal retention of excess dietary sodium (Bakris & Mensah, 2002), vascular hypertrophy (Bakris & Mensah, 2002), increased sympathetic activity (Bakris & Mensah, 2002; Weber, 1995), abnormal renin-angiotensin system (Bakris & Mensah, 2002; Weber, 1995), hyperinsulinemia (Cardillo, Kilcoyne, Nambi et al., 1998) and endothelial cell dysfunction (Bakris & Mensah, 2002; Weber, 1995; Cohn, 1999), have all been suggested as possible factors in the development of hypertension.

Genetic alterations may initiate the processes that lead to permanent hypertension (Kaplan, 2001). It is estimated that 30-60% of the variation in BP between individuals is due to genetic factors (Bakris & Mensah, 2002; Hagberg, Park, & Brown, 2000; Weber, 1995). Current evidence suggests that the hypertensive phenotype is likely caused by multiple genes (Lifton, Gharavi, & Geller, 2001). Genetic alterations in angiotensinogen (Caulfield, Lavender, Farrall et al., 1994; Hagberg, Park, & Brown, 2000) and nitric oxide (NO) may increase an individuals risk for developing hypertension (Bakris & Mensah, 2002). Altered angiotensinogen could lead to abnormalities of the renin-angiotensin system resulting in increased activity of renin, and ultimately an elevated blood pressure (Neutel, Smith, Graettinger et al., 1992). Reduced NO release could result in elevated ABPs due to decreased renal blood flow, increased tubular reabsorption in the kidneys, elevated vasoconstriction effect of angiotensin II, activation of the RAAS and/or enhanced vascular response to vasoconstrictors (Granger & Alexander, 2000). The difficulty is that the same genetic phenotype may manifest itself differently in different environments (Bakris & Mensah, 2002).

A strong association between low birth weight and hypertension has been found, however the mechanisms have not yet been determined (Irving, Shore, Belton et al., 2004; Lackland, Egan, & Ferguson, 2003; Law & Shiell, 1996). Reduced nephrogenesis with a greater threshold for pressure natriuresis and/or increased sensitivity to glucocorticoids have been discussed as potential mechanisms underlying this relationship (Lackland, Egan, & Ferguson, 2003).

Impairments in the excretion of salt may play a role in the development of hypertension (Bakris & Mensah, 2002). Decreased responsiveness of the kidneys to atrial natriuretic hormone (Richards, 1994) and nephron heterogeneity (Sealey, Blumenfeld, Bell et al., 1988) may result in excess sodium retention and therefore increased fluid retention and volume. Investigators have found that individuals with sodium sensitivity have greater vascular complications than those who are not as sodium sensitive (Weinberger, 1996). Individuals who respond to modifications in dietary sodium intake with alterations in ABP are considered salt sensitive (Weinberger, 1996).

Vascular remodelling is believed to be an adaptive process which normalizes increased wall stress, and plays a role in the maintenance of hypertension (Bakris & Mensah, 2002). The increased wall stress stimulates growth factors that result in vascular structural changes such as increased arterial wall thickness and reduced lumen diameter. These structural changes increase peripheral resistance and reinforce and perpetuate high arterial blood pressure levels (Tanaka, Reiling, & Seals, 1998). Many vasoconstrictors such as angiotensin II and endothelin also have significant growth and remodelling properties (Bakris & Mensah, 2002; Cohn, 1999; Weber, 1995). Vasodilators such as nitric oxide tend to be inhibitors of growth promotion and remodelling, therefore consistent perturbations in the normal balance of vasoconstrictors and dilators caused by changes in blood pressure, hormonal levels and endothelial dysfunction can result in an excess of growth promoters over inhibitors and result in abnormal vascular remodelling (Bakris & Mensah, 2002; Cohn, 1999).

Numerous studies have documented a hyperactive SNS in primary hypertension, especially in young or borderline hypertensives (Bakris & Mensah, 2002). Elevated plasma norepinephrine levels, elevated plasma renin levels, increased heart rate, systemic vascular resistance and vascular reactivity often reflect elevated SNS activity (Bakris & Mensah, 2002). A defect in baroreceptor sensitivity has been postulated to contribute to the increased BP variability in hypertensive individuals (Bakris & Mensah, 2002). Increased levels of sympathetic nerve activity associated with hypertension can result in vascular constriction or by increasing cardiac output (Kaplan, 2001). The origin of these variations in SNS activity remains to be determined.

The renin-angiotensin system is one of the most important mechanisms in the regulation of blood pressure and blood volume (Bakris & Mensah, 2002). In the majority of hypertensive patients, renin activity varies from normal to low (Bakris & Mensah, 2002). Varying renin levels in hypertension may reflect a combination of excess renin activity due to nephron ischemia and reduced renin activity due to hyperfiltering nephrons (Sealey, Blumenfeld, Bell et al., 1988).

Circulating insulin has an isolated vasoconstrictor effect on vascular smooth muscle and exerts vasodilatory effects through nitric oxide in normal humans (Cardillo, Kilcoyne, Nambi et al., 1998). Individuals with hypertension may experience a slight imbalance between the sympathetic and vascular actions of insulin resulting in an augmented pressor action and impaired vasodilatory effect due to insulin resistance often associated with obese hypertensive individuals (Cardillo, Kilcoyne, Nambi et al., 1998).

Reduced peripheral vasodilation may occur due to endothelial cell dysfunction and impaired production of nitric oxide (Cohn, 1999; Ruschitzka, Corti, Noll et al., 1999). The release of nitric oxide from the endothelium functions to maintain low arterial tone and prevent smooth muscle hypertrophy. Impaired nitric oxide release results in increased vascular resistance associated with hypertension (Cohn, 1999; Rudic, Shesely, Maeda et al., 1998).

Despite a variety of potential mechanisms, hypertensive individuals are lacking an appropriate compensatory mechanism to normalize the changes in TPR and/or cardiac output and return BP levels to the normal range (Bakris & Mensah, 2002). The list of possible mechanisms contributing to the development of hypertension continues to be examined.

2.3.3 Consequences/Complications of Hypertension

Target organ damage occurs in hypertensive individuals due to chronically elevated ABP levels (Bakris & Mensah, 2002). It is believed that high ABP increases the risk of cardiovascular events because of the vascular injury associated with elevated blood pressures (Cohn, 1999). Much of the premature death and disability attributable to hypertension can be prevented by effective control of systolic and diastolic BP (Mensah, 2002). These benefits have been found in all populations studied and in developed, as well as developing countries (Mensah, 2002). Unfortunately control rates of hypertension are slowing, with little improvement in treatment and awareness around the world (Mensah, 2002).

Vascular complications associated with hypertension can be generally classified as hypertensive or atherosclerotic (Kaplan, 2001). Hypertensive complications, such as hemorrhagic stroke, congestive heart failure and renal failure (Kannel, Gordon, & Schwartz, 1971; Stewart, 1992), are directly caused by the increased blood pressure and can be prevented by reducing arterial blood pressure to normal levels (Kaplan, 2001). Hemorrhagic strokes, aortic aneurysms and renal failure may occur due to weakening of the blood vessels under high pressures, while the increased workload on the myocardium with elevated arterial blood pressures may lead to left ventricular hypertrophy (Cononie, Graves, Pollock et al., 1991; Turner, Spina, Kohrt et al., 2000) and eventually heart failure.

Atherosclerotic complications such as coronary heart disease (CHD) and peripheral vascular disease (PVD) have multiple causes (Kannel, Gordon, & Schwartz, 1971; Stewart, 1992). Hypertension may be the most significant risk factor for atherosclerosis, because of its damaging effect on the endothelium, however the disease process may not be arrested with a reduction of ABP levels (Kaplan, 2001).

2.3.4 Treatment of hypertension

Due to the variable nature of hypertension, similar blood pressure values are associated with different consequences in different patients (Resnick & Lester, 2002). Treatment of hypertension is not solely based on blood pressure values, but on the overall cardiovascular risk profile and biological aggressiveness of the high blood pressure (Kaplan, 2001).

The goal of therapeutic interventions to lower blood pressure is to reduce the risk of cardiovascular disease (Cohn, 1999; Hagberg, Park, & Brown, 2000), improve quality of life and reduce the risk of premature disability and death (Bakris & Mensah, 2002) by preventing the accelerated increase of SBP (Safar & Laurent, 2003). The majority of hypertension can be easily diagnosed and controlled (Mensah, 2002). Unfortunately, a large number of hypertensive individuals remain inadequately treated or receive no treatment at all (Weber, 1995). Proper treatment of hypertension is difficult because of the nature of the disease. Not only is hypertension induced by common, unhealthy lifestyles, it is often asymptomatic with a delay in consequences of 10 to 30 years (Kaplan, 2001).

The complexity of hypertension suggests that a combination drug therapy is likely to be more effective than single drug treatment for moderate to severe hypertension (Bakris & Mensah, 2002; Stewart, 1992). Beta-blockers and diuretics are the older classes of drugs commonly prescribed for their antihypertensive actions, however the training effects of exercise are reduced with beta blockade (Petrella, 1998). Newer classes of drugs include ACE inhibitors and calcium channel blockers (Weber, 1995). Exercise may decrease the amount and frequency of doses needed to lower BP (Petrella, 1998). Although diagnosed with hypertension, not all patients will need pharmacological therapy, depending on their risk factor profile (Kaplan, 2001).

Current treatment guidelines emphasize the role of non-pharmacological interventions, including physical activity, for the treatment of hypertension (Hagberg, Park, & Brown, 2000). Each treatment plan must be based on the individual patient,

however all patients should be strongly advised to modify their lifestyle and environment accordingly. A slow and gradual implementation of any lifestyle change may help with patient adherence and interest. Continued education concerning the importance of behavioural change and lifestyle modifications must be provided in supportive environments to benefit the population at large (Mensah, 2002).

Many practitioners do not advocate for non-drug therapies due to the meagre amount of firm evidence that these alternate therapies are effective and realistic. However hypertension is becoming more prevalent and difficult to treat as the population ages (Kokkinos, Narayan, & Papademetriou, 2001). With greater use of pharmacological aides the incidence of side effects increases and reduced compliance becomes more of an issue, therefore the addition of lifestyle modifications such as exercise may be able to lower BP at lower doses of medications and reduce adverse effects (Kokkinos, Narayan, & Papademetriou, 2001).

Avoidance of tobacco, reduction in weight, salt restriction, exercise and relaxation are some of the most common lifestyle modifications advised to individuals with hypertension (Kaplan, 2001). The effectiveness of exercise in reducing BP can allow individuals to take less medication without compromising adequate control of BP (Kokkinos, Narayan, & Papademetriou, 2001).

2.3.5 Exercise and Hypertension

Individuals who exercise regularly, benefit from increased work capacity, improved cardiac risk profiles and better control of CAD symptoms (Stewart, 1992). Approximately 75% of hypertensive individuals who exercise will reduce blood pressure

with exercise treatment (Hagberg, Park, & Brown, 2000). Pathophysiology and genetic differences in hypertensive individuals may be the reason for the variations in blood pressure responses to exercise (Wallace, 2003).

If a reduction in blood pressure occurs in a hypertensive individual in response to exercise training, there must be a decrease in cardiac output and/or total peripheral resistance. Some investigators report a reduction in cardiac output (Hagberg, Montain, Martin, III et al., 1989), a reduction in TPR (Tanaka, Reiling, & Seals, 1998) or no change in either (Cononie, Graves, Pollock et al., 1991). The mechanisms underlying the cardiovascular changes are not completely understood and are likely a complex combination of metabolic, cardiovascular and neural factors in addition to changes in skeletal muscle fiber type (Pagani, Somers, Furlan et al., 1988). It is currently believed that exercise training acts through a number of mechanisms to lower resting arterial pressure (Kokkinos, Narayan, & Papademetriou, 2001). Generally investigators believe that the reductions in BP are independent of body weight (Hagberg, Park, & Brown, 2000; Wallace, 2003), body composition (Hurley, Hagberg, Goldberg et al., 1988; Wallace, 2003) or antihypertensive medications (Wallace, 2003). Several mechanisms have been proposed including changes in sympathetic nervous system activity (Pagani, Somers, Furlan et al., 1988; Seals & Hagberg, 1984), genetics (Hagberg, Park, & Brown, 2000), improved endothelial functioning (Kokkinos, Narayan, & Papademetriou, 2001), plasma norepinephrine levels (Kokkinos, Narayan, & Papademetriou, 2001), and/or arterial restructuring (Tanaka, Reiling, & Seals, 1998).

2.3.5.1 Aerobic Exercise

Aerobic exercise consists of repetitive low-resistance movements such as walking or cycling that last for more than 10 minutes (Kokkinos, Narayan, & Papademetriou, 2001). These activities increase the demand for oxygen resulting in better distribution of cardiac output, more oxygen extraction from a given blood flow by the muscles and lower heart rate and blood pressure at rest (Stewart, 1992). Aerobic exercise training is considered the most effective mode of exercise in the prevention and treatment of hypertension (Nicholls, 1990; Wallace, 2003). The average blood pressure reduction for hypertensive individuals following aerobic exercise treatment is 11mmHg for systolic and 8mmHg for diastolic blood pressure (Hagberg, Park, & Brown, 2000; Kokkinos, Narayan, & Papademetriou, 2001). In a review of 21 exercise studies using aerobic exercise to alter blood pressure, Kokkinos et al. (2001) concluded that the average reductions for the control groups were 4 mmHg and 1.3 mmHg for systolic and diastolic blood pressures respectively.

Despite the well-established benefits of regular aerobic exercise, it is underutilized as non-pharmacological treatment of hypertension mainly because of the poor understanding of exercise and the interaction of frequency, intensity, and duration to achieve BP reductions (Kokkinos, Narayan, & Papademetriou, 2001). The exercise-training program for optimal benefits should consist of an individualized program 3-5 times a week for 30 to 60 minutes at 50-80% predicted max heart rate (Kokkinos, Narayan, & Papademetriou, 2001; Petrella, 1998). A frequency of three times a week, alternating exercise and non-exercise days is considered the minimum for blood pressure

reduction (Kokkinos, Narayan, & Papademetriou, 2001; Wallace, 2003). Low intensity exercise is more effective at lowering blood pressure than high intensity exercise (Motoyama, Sunami, Kinoshita et al., 1998), therefore it has been suggested that the intensity be low to moderate (Kokkinos, Narayan, & Papademetriou, 2001; Petrella, 1998). This is important for hypertensive individuals because low intensity exercise has a lower risk for cardiac complications, physicians may feel more comfortable prescribing low intensity versus high intensity exercise and patients may be more inclined to follow the program (Kokkinos, Narayan, & Papademetriou, 2001). Investigators have found that exercise programs are effective at lowering BP in hypertensive individuals of advanced age. Cononie et al. (Cononie, Graves, Pollock et al., 1991) reported reductions of 8 mmHg for systolic, 9mmHg for diastolic and 8 mmHg for mean arterial pressure in a group of 70-79year old hypertensive individuals after 6 months of aerobic exercise. In a similar study, Motoyama and colleagues (Motoyama, Sunami, Kinoshita et al., 1998) found reductions of 15mmHg for systolic, 9mmHg for diastolic and 11mmHg for mean blood pressure in 68-84 year old hypertensive individuals. Other benefits of endurance exercise for hypertensive patients include improvement of the plasma lipoprotein-lipid profile, increase in insulin sensitivity, improvement in left ventricular hypertrophy (Turner, Spina, Kohrt et al., 2000), resulting in an overall reduction in cardiovascular risk (Hagberg, Park, & Brown, 2000).

2.3.5.2 Resistance Exercise

Strength training is considered a promising intervention for reversing the loss of muscle function and muscle deterioration with age (Hurley & Roth, 2000; Martel,

Hurlbut, Lott et al., 1999). Recently the effects of resistance training on the risk factors for CAD have been examined, including the effects of strength training on blood pressure in individuals with high normal values (Martel, Hurlbut, Lott et al., 1999). Resting BP increases with age and elevated blood pressure is considered a major cardiovascular risk factor in the elderly. In the past resistance training has been contraindicated for hypertensive individuals because of the excessive pressor load on the heart (Ray & Carrasco, 2000; Stewart, 1992; Wallace, 2003). In a review of progressive resistance training studies with a minimum duration of 4 weeks, Kelley and Kelley (2000) found that resistance training results in reductions in resting systolic blood pressure of 2 percent and a 4 percent decrease in diastolic blood pressure. Resistance exercise appears to be an effective method for reducing high blood pressure without exacerbating the blood pressure response in hypertensive individuals or inducing hemodynamic or left ventricular abnormalities (Kelley & Kelley, 2000). Hurley and colleagues (Hurley, Hagberg, Goldberg et al., 1988) found that resistance training can lower risk factors for CAD, including lowering BP, independent of changes in VO_2 max, body weight or body composition.

Resistance, or weight training is the mode of exercise performed to increase muscle endurance, power and muscle strength (Stewart, 1992; Wallace, 2003). Weight training at moderate levels is considered a safe, low-risk activity for individuals with good left-ventricular function (Stewart, 1992). Conventional weight training uses slow movements against high resistance with few repetitions and a large static component (Stewart, 1992). The response to this type of exercise is preferable for competitive lifters,

but for more recreational exercise, circuit weight training (CWT) is preferred (Stewart, 1992). In circuit weight training individuals use a moderate amount of weight to perform several repetitions in a continuous fashion with minimal rest between the 10-12 stations (Gettman, Ayres, Pollock et al., 1978). A CWT program at 30-50% of one-repetition maximum does not exacerbate HR or BP responses or provoke more ischemia or arrhythmias than does aerobic exercise (Stewart, 1992). By using weights in an aerobic manner, CWT improves cardiovascular endurance and muscle strength simultaneously (Stewart, 1992). However, no differences were found for changes in resting blood pressure studies comparing circuit weight training to a traditional program in meta-analytic review (Kelley & Kelley, 2000). More traditional resistance training with heavier weights results in large acute increases in systolic and diastolic blood pressure (Kelley & Kelley, 2000; MacDougall, Tuxen, Sale et al., 1985).

The information available on the effects of resistance training on resting blood pressure is limited and unequivocal. A possible antihypertensive effect has been suggested by some investigators (Blumenthal, Siegel, & Appelbaum, 1991; Harris & Holly, 1987; Hurley, Hagberg, Goldberg et al., 1988) but not by others (Cononie, Graves, Pollock et al., 1991). Harris and Holly (1987) and Hurley and colleagues (1988) found significant reductions in diastolic BP of 5mmHg after 16 weeks of high-intensity resistive training. In contrast, Blumenthal and colleagues (Blumenthal, Siegel, & Appelbaum, 1991) found a reduction of 7mmHg for SBP and 6mmHg for DBP after 16 weeks of circuit weight training, which were similar to the control group and aerobically trained group. No significant changes in BP were found in a group of 70-79 year old men and

women after 6 months of training, however resistance training did not adversely affect blood pressure (Cononie, Graves, Pollock et al., 1991). Consequently, although resistance exercise is not considered the preferred primary mode of exercise for blood pressure reduction, it should be included as part of a regular exercise program (Kokkinos, Narayan, & Papademetriou, 2001; Wallace, 2003).

2.3.5.3 Isometric Exercise

Limited investigations have occurred examining the effects of isometric training on resting blood pressure (Ray & Carrasco, 2000; Taylor, McCartney, Kamath et al., 2003; Wiley, Dunn, Cox et al., 1992). The earliest study of isometric efforts reported reduction in blood pressures after 5-8 weeks of isometric training with the whole body (Kiveloff & Huber, 1971). Buck and Donner (Buck & Donner, 1985) provided further support for a hypotensive effect of isometric training after their epidemiologic observations in the workplace indicated that the incidence of hypertension was reduced in individuals whose occupations included a larger amount of isometric effort.

A reduction in SBP was found in normotensive individuals after 5 weeks of isometric leg training and 5 weeks of isometric arm training as compared to the non-exercising controls (Howden, Lightfoot, Brown et al., 2002). In contrast, Somers and colleagues (1992) did not find an attenuation in blood pressure after 6 weeks of isometric handgrip training. Inaccurate blood pressure techniques (sphygmomanometry) and lack of power of the investigation (n=5) were suggested as potential reasons for the non-significant findings. The limited evidence that ABP is attenuated in normotensive individuals raises the questions as to whether isometric training would be beneficial for

individuals with hypertension. The evidence from Wiley and colleagues (Wiley, Dunn, Cox et al., 1992) supported the use and efficacy of isometric training in the reduction of resting arterial BP for individuals with hypertension, suggesting that 5 and 8 weeks of submaximal interrupted isometric handgrip training can reduce resting blood pressure in healthy volunteers with high-normal blood pressure.

Several potential mechanisms for the change in arterial BP after isometric exercise have been proposed and investigated (Ray & Carrasco, 2000; Taylor, McCartney, Kamath et al., 2003). Taylor and colleagues concluded that 10 weeks of isometric handgrip training at 30% MVC was able to elicit reductions in blood pressure and an increase in parasympathetic modulation measured with spectral analysis in older adults with isolated systolic hypertension (Taylor, McCartney, Kamath et al., 2003). The decrease in muscle sympathetic nerve activity (MSNA) has been found in the peroneal nerve without a parallel reduction in BP after 6 weeks of unilateral handgrip in healthy subjects (Somers, Leo, Shields et al., 1992). Further investigation of possible mechanisms examined the effects of muscle sympathetic nerve activity (MSNA) after five weeks of isometric handgrip training and concluded that although DBP and MAP decreased significantly, there was no change in MSNA following training (Ray & Carrasco, 2000).

It has also been proposed that the increased exposure to shear stress with isometric training may improve endothelial function, and/or sympathetic outflow may be altered to other vascular beds besides the skeletal muscle (Ray & Carrasco, 2000). The consistent hypotensive effect of isometric training on resting arterial pressure suggests the usefulness of isometric training at moderate levels in the treatment of hypertension,

however further investigations into the mechanisms responsible for this change are required.

2.4 Arterial Structure

The arterial system is designed to deliver an adequate supply of blood to the different tissues and to transform the pulsatile flow from the heart to a continuous flow in the periphery (Benetos, Laurent, Asmar et al., 1997a). Arteries are classified as elastic, muscular and arterioles (Seeley, Stephens, & Tate, 2003). The walls of each type of artery are composed of three layers; the intima, the media and the adventitia. The innermost layer, the intima is composed of endothelial cells, a thin layer of connective tissue and a layer of elastic fibres. The media regulates blood flow with the layer of circularly arranged smooth muscle cells, collagen and elastin. An external elastic membrane separates the media from the adventitia (Mulvany, 1990). The adventitia, the outermost layer, is composed primarily of connective tissue, with a dense area near the media that becomes more loose as the tissue merges with the surrounding connective tissues (Seeley, Stephens, & Tate, 2003). The composition of each layer depends on the diameter and type of blood vessel (Mulvany, 1990).

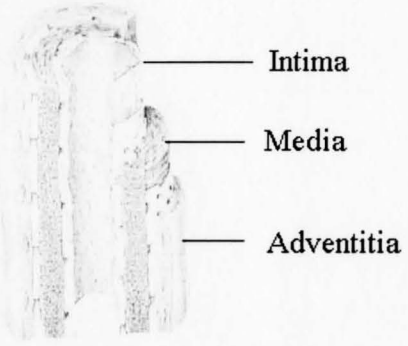


Figure 1.1 Composition of a muscular artery. (Adapted from Principles of Anatomy and Physiology, 10th Edition, Tortora and Grabowski, John Wiley and Sons, 2003)

The large elastic arteries have the largest diameter and the greatest amount of elastic tissue to assist in their role as conducting arteries (Mulvany, 1990; Seeley, Stephens, & Tate, 2003). A thick intima, small amounts of smooth muscle, and thin adventitia are all characteristics of elastic arteries (Seeley, Stephens, & Tate, 2003). Some of the most significant changes with aging occur in elastic arteries, including a reduction in elasticity and thickening of the intima (Seeley, Stephens, & Tate, 2003).

Muscular arteries are the distributing arteries with thick walls to control blood flow to areas of the body (Seeley, Stephens, & Tate, 2003). The walls are thick compared to their diameter because of the 25-40 layers of smooth muscle in the media. Muscular arteries have a well developed internal elastic membrane of the intima and a thick layer of collagenous connective tissue in the adventitia (Seeley, Stephens, & Tate, 2003). The changes with age in muscular arteries are less dramatic than elastic arteries, often not even affecting blood vessel function (Seeley, Stephens, & Tate, 2003).

Hypertension is associated with an increase in vascular tone and vascular structural abnormalities (Cohn, 1999). The increase in blood pressure and hormones that induce vasoconstriction tend to stimulate arterial growth of smooth muscle cells and connective tissue (Cohn, 1999). The structural changes associated with hypertension could be a distinguishing feature between normotensive and hypertensive individuals, perhaps even identifying those at risk for future hypertension (Cohn, 1999). Unfortunately these changes are similar to those that occur with aging, making it difficult to distinguish between the two. Changes in tone and structure of the arterial wall should alter the function of the wall in ways that could be monitored clinically (Cohn, 1999). Therefore it is important to understand the physiologic effects of the arterial wall changes.

2.5 Arterial Compliance

Arterial compliance is the extent of increase in arterial dimension in response to an increase in pressure (Cohn, 1999). The compliance of an artery varies with pressure; as pressure rises, the compliance of an artery decreases and vice versa. Arterial compliance is the arterial characteristic that allows blood to flow through the arterial tree during systole and diastole (Guyton & Hall, 1996), by expanding to buffer the flow during systole and recoiling during diastole (Miyachi, Donato, Yamamoto et al., 2003; Seals, 2003). Less compliant arteries can lead to high SBP due to an inability to distend properly, and a low DBP as a result of impaired contraction (Weber, 2001), thereby increasing pulse pressure. Elevated SBP contributes to increased ventricular afterload while reduced DBP may impair coronary perfusion (Ferrier, Waddell, Gatzka et al., 2001; McVeigh, Bratteli, Morgan et al., 1999).

The reduction in arterial compliance has been deemed an independent risk factor for the development of cardiovascular disease (Rowe, 1987). A further increase in arterial stiffness is found in individuals with coronary artery disease, higher blood glucose levels, excess cholesterol and with the presence of heart failure (Benetos, Waeber, Izzo et al., 2002). It has not been determined if altered pulsatile characteristics of the arterial circulation precede the development of/or are a consequence of cardiovascular disease (McVeigh, Bratteli, Morgan et al., 1999). The process of atherosclerosis contributes to the increase in collagen content and calcification of the vessels. If atherosclerosis is present in advanced age and/or hypertension, arterial compliance may be further decreased (Benetos, Laurent, Asmar et al., 1997a).

Reduced arterial compliance has a number of adverse effects including elevations in SBP and PP and increased left ventricular wall tension (Miyachi, Donato, Yamamoto et al., 2003). Chronic increases in SBP and PP cause vascular endothelial damage and accelerate atherosclerosis, increasing the risk of cerebrovascular, coronary and peripheral vascular diseases (Seals, 2003). Reduced arterial compliance can also contribute to ventricular hypertrophy, valvular dysfunction and heart failure (Rowe, 1987). Less compliant vessels may also impair baroreflex sensitivity (Monahan, Dinenno, Seals et al., 2001; Seals, 2003). If the vessels are stiffer, then for any given change in pressure there would be less afferent firing from the baroreceptors, less inhibition of sympathetic outflow and less increase in vagal tone resulting in greater ABP variability (Joyner, 2000).

2.5.1 Measurement of arterial compliance

A number of different methods have been developed to assess the changes in arterial diameter and pressure relating to arterial compliance. Microvessels obtained by buttocks biopsy in man has provided direct measurements of arterial wall structure and function, however this technique is only useful for small vessels and is not practical for routine screening (Cohn, 1999). Indirect measurements of arterial compliance are most often performed non-invasively using ultrasound imaging with simultaneous blood pressure measurements or via the pulse wave velocity (PWV) method.

Ultrasound imaging in conjunction with arterial tonometry provides a non-invasive technique of measuring functional arterial compliance by evaluating structural characteristics with concurrent measures of blood pressure in superficial arteries (Arnett, Chambless, Kim et al., 1999). Measurement of arterial compliance in specific central and peripheral arteries such as the carotid or brachial artery can be acquired with this method of analysis. Ultrasound imaging allows for tracking of the arterial wall to determine arterial diameter during the cardiac cycle. Arterial tonometry allows for an accurate, non-invasive method for determining continuous blood pressure measurements (Kelly, Hayward, Avolio et al., 1989) at the same site as the diameter recordings. One method of arterial tonometry utilizes a pencil type probe positioned over the artery of interest to record uncalibrated continuous blood pressure measurements. Calibration of the pencil type probe can occur by including continuous blood pressure measurements with an arterial tonometer at the radial artery with a cuff measurement of blood pressure at the brachial artery. A potential concern with the ultrasound/arterial tonometer method of

arterial compliance measurement is that the investigators require more training for accurate, reproducible recordings of both the ultrasound images and arterial tonometry signal. Accurate recordings can be difficult in obese individuals with larger amounts of tissue surrounding the arteries. Pulsewave velocity is defined as the distance traveled by a pressure wave divided by the time of that transmission (Cohn, 1999). It is inversely related to arterial compliance; the slower the velocity the greater the compliance. This method of determining arterial compliance has been considered the best and is most often used by investigators as it requires less training than ultrasound and arterial tonometry. Practical concerns with PWV occur when the points of measurement along the arterial tree are not in line with each other (O'Rourke, Staessen, Vlachopoulos et al., 2002). Determining the actual distance between arteries can also be a problem as measurements are made on the surface of the body and anatomical differences may alter the length of arteries between individuals (O'Rourke, Staessen, Vlachopoulos et al., 2002). Different structural compositions may alter PWV measurements as central, more elastic arteries are modified with aging, yet the more muscular peripheral arteries do not show these age-dependant changes.

2.5.2 Mechanisms of Reduced Arterial Compliance

The composition of blood vessels influences the compliance of the vessel wall (Cox, 1981). A variety of changes in arterial structure and mechanics contribute to reduced arterial compliance, however the exact mechanisms are still incompletely understood. Some of the structural induced changes in arterial compliance that have been discussed include medial hypertrophy, increased content of vascular smooth muscle, and

changes in the elastin-collagen ratio (Cox, 1981; Joyner, 2000; Safar, Laurent, Pannier et al., 1987). The most reasonable explanations for direct arterial wall effects appear to be changes in smooth muscle tone due to hypertrophy, hyperplasia, increased alpha-adrenergic stimulation and/or reduced nitric oxide bioavailability (Seals, 2003), collagen cross-linking (Hagberg, Montain, Martin, III et al., 1989), and deterioration in elastin fibers (Ferrier, Waddell, Gatzka et al., 2001). The mechanical effect of elevated pressure on arteries dilates and stiffens arteries by stretching their walls (Armentano, Megnien, Simon et al., 1995).

The two major factors leading to arterial compliance are older age and hypertension (Benetos, Laurent, Asmar et al., 1997b; Dart, Gatzka, Cameron et al., 2004). The main age-related changes, diameter enlargement and elastin breakdown, are a result of tissue fatigue (Benetos, Laurent, Asmar et al., 1997a). Hypertrophy and collagen accumulation due to the increased mechanical stress are the primary alterations with hypertension (Cox, 1981). In hypertensive individuals, active mechanisms within the arterial wall are involved because the diameter of peripheral muscular arteries remains unchanged, despite an elevated BP, while the central arteries increase their diameter in proportion to the increase in BP (Benetos, Waeber, Izzo et al., 2002). The central arteries in elderly hypertensives also exhibit medial hypertrophy associated with development of the extracellular matrix of the media and the adventitia not found in peripheral arteries (Benetos, Waeber, Izzo et al., 2002). The question remains as to whether the vascular arterial changes associated with hypertension are the cause or result of elevated BP (Cox, 1981). Changes in endothelial function occur with aging and hypertension, although the

location within the arterial tree may differ (Benetos, Waeber, Izzo et al., 2002). The mechanisms that occur with aging are likely accelerated with hypertension (Ferrier, Waddell, Gatzka et al., 2001).

2.5.3 Arterial Compliance and Aging

As individuals age, the large conducting vessels become less compliant and lose their ability to respond to changes in pressure (Dart & Kingwell, 2001; Hagberg, Montain, Martin, III et al., 1989; Joyner, 2000). This increase in stiffness has been described in both healthy and diseased populations (Benetos, Waeber, Izzo et al., 2002; Tanaka, Dinenno, Monahan et al., 2000). A 40-50% reduction in carotid arterial compliance has been observed in healthy sedentary individuals between the ages of 25 and 75 (Tanaka, Dinenno, Monahan et al., 2000). Central, elastic arteries stiffen progressively with age, whereas the stiffness of muscular arteries changes little (Benetos, Laurent, Asmar et al., 1997b; Seals, 2003). However, there is considerable individual variability with respect to the effect of age on arterial compliance (McVeigh, Bratteli, Morgan et al., 1999). The extent of the reduced arterial compliance with aging may depend on several environmental or genetic factors (Benetos, Waeber, Izzo et al., 2002; Safar & Laurent, 2003). Individual differences in sodium intake and sensitivity and variations in the genotype for the angiotensin II type 1 receptor may influence the development of arterial compliance with aging (Benetos, Waeber, Izzo et al., 2002; Safar & Laurent, 2003). In larger arteries, aging results in alterations of endothelial function, fraying and fragmentation of elastin and an increased number and cross-linking of collagen fibers (Joyner, 2000).

2.5.4 Arterial Compliance and Hypertension

Arterial compliance has been found to be significantly reduced in patients with either systolic hypertension or sustained hypertension (Dart & Kingwell, 2001; Safar, Laurent, Pannier et al., 1987; Weinberger, Fineberg, & Fineberg, 2002a). The association between compliance and hypertension has been identified through observations of elevated pulse pressure in hypertensive individuals (Asmar, Rudnichi, Blacher et al., 2001). These indicators of reduced compliance were considered to reflect abnormalities in the intrinsic properties of the arterial wall because the pulse pressure elevations made in the face of unaltered MAP versus controls (Safar, Laurent, Pannier et al., 1987). More direct evidence of a relationship between hypertension and decreased compliance has been obtained through the application of arterial PWV and ultrasound assessment techniques (Armentano, Megnien, Simon et al., 1995; Ferrier, Waddell, Gatzka et al., 2001; Miyachi, Donato, Yamamoto et al., 2003; Sinoway, Shenberger, Wilson et al., 1987; Tanaka, Dinenno, Monahan et al., 2000).

The primary structural modification of the vessel wall in individuals with hypertension is hypertrophy of the medial smooth muscle layer (Benetos, Waeber, Izzo et al., 2002). Growth of both vascular smooth muscle and connective tissue can occur due to hemodynamic (Cohn, 1999), neural (Damon, 2000) and hormonal influences (Cohn, 1999; Damon, 2000). Variations in the genes for aldosterone synthase and angiotensin II type I receptors are associated with an augmented response to angiotensin II resulting in increased arterial stiffness in hypertension as compared to normotensive individuals (Benetos, Gautier, Ricard et al., 1996; Benetos, Waeber, Izzo et al., 2002).

2.5.5 Pharmacological Treatment of Impaired Arterial Compliance

Pharmacological treatment of hypertension can have varying effects on arterial stiffness depending on the antihypertensive medication protocol applied (Benetos, Laurent, Asmar et al., 1997a). Arterial compliance can be improved with the use of common antihypertensive medications; calcium channel blockers, ACE inhibitors and/or antiotensin II receptor antagonists, and nitrates (Resnick & Lester, 2002). No improvement in arterial compliance is usually observed with selective beta-blocker therapy (Benetos, Laurent, Asmar et al., 1997b; Resnick & Lester, 2002). Diuretics and non selective beta blockers also induce minor changes in arterial compliance (Benetos, Laurent, Asmar et al., 1997a). Even though the exact mechanisms for these differences are not understood, use of these drugs for treatment of hypertension may result in greater clinical benefits for the hypertensive patient.

2.5.6 Exercise and Arterial Compliance

2.5.6.1 Aerobic Exercise

The benefits of aerobic exercise for cardiovascular risk reduction occur in part due to modification of arterial properties (Bertovic, Waddell, Gatzka et al., 1999). Recent evidence indicates that regular aerobic exercise attenuates age-associated reductions in large artery compliance and partially restores compliance in previously sedentary middle-aged and older adults (Tanaka, Dinenno, Monahan et al., 2000). Tanaka and colleagues (2000) found that the age-associated loss of central arterial compliance can be partially restored after just 3 months of brisk walking, a level of exercise that most middle aged and healthy adults should be able to perform. The 25% increase in arterial compliance

with this walking program was not associated with changes in body mass, adiposity, arterial blood pressure, plasma cholesterol or maximal aerobic capacity (Tanaka, Dinenno, Monahan et al., 2000). With a cross-sectional design, Tanaka and colleagues (2000) were able to determine that recreational exercise improved arterial compliance, but to a lesser extent than vigorous exercise. An improvement in arterial compliance was also found by Monahan and colleagues (2001) after 13 weeks of home-based walking or walk-jogging at 60-85% maximal heart rate in previously sedentary middle-aged and older men. The improvement in compliance was associated with an improvement in baroreflex sensitivity, supporting an independent association between the two (Monahan, Dinenno, Seals et al., 2001). In contrast, an eight-week cross-over study of aerobic exercise and sedentary activities did not modify central arterial compliance in individuals with chronically elevated SBP even though an improvement in aerobic and maximum work capacity occurred (Ferrier, Waddell, Gatzka et al., 2001). The absence of improvements in arterial compliance may have occurred due to the resistance of the large-artery stiffness to adapt to short term aerobic exercise in the absence of alterations in BP (Ferrier, Waddell, Gatzka et al., 2001).

A longitudinal examination of arterial stiffness and cardiorespiratory fitness found that improving VO_2max and physical activity levels reduced muscular and elastic arterial stiffness (Ferreira, Twisk, Stehouwer et al., 2003). Increased shear forces present during aerobic exercise may improve muscular artery function by improving nitric oxide release and increasing arterial diameter (Ferreira, Twisk, Stehouwer et al., 2003). Physical activity levels were associated with reduced arterial stiffness independently of

VO_2max indicating that lower intensity activities may be sufficient for improvements in arterial stiffness (Ferreira, Twisk, Stehouwer et al., 2003). Although the evidence is mixed, aerobic exercise may be an effective lifestyle intervention for reducing the loss of age-associated arterial compliance if started at a younger age and continued longer-term (Kingwell, 2002).

Exercise training can modify the changes in arterial structure that lead to reduced arterial compliance in several ways. The increase in arterial pressure and heart rate associated with exercise may lead to periods of increased deformation of the large blood vessels, and reduced or modified cross-linking of the connective tissue (Joyner, 2000). Direct relaxation of vascular smooth muscle (Tanaka, Dinenno, Monahan et al., 2000) and/or direct inhibition of vascular smooth muscle hypertrophy may occur due to upregulation of nitric oxide, and other vasodilators as a result of increased pulsatile flow with exercise (Joyner, 2000). It is unlikely that changes in elastin-collagen composition occurred with short-term aerobic exercise because structural changes take years to occur (Tanaka, Dinenno, Monahan et al., 2000). The decline in baroreflex sensitivity observed with aging was significantly attenuated in endurance trained healthy men (Monahan, Dinenno, Seals et al., 2001). This improvement in cardiovagal baroreceptor response was explained by the improvements in carotid arterial compliance (Monahan, Dinenno, Seals et al., 2001). An improvement in the ability of the carotid artery to adapt to changes in pressure would allow the baroreceptors in the carotid arch to respond to the alterations in pressure more effectively.

2.5.6.2 Resistance Training

Interest in the effects of resistance training on arterial compliance has increased over the last few years as strength training has been recommended as a part of a preventative and rehabilitative training program (Miyachi, Donato, Yamamoto et al., 2003). Limited data exists surrounding the effects of resistance training on arterial compliance. High-resistance strength training has been associated with a reduction in arterial compliance and elevation in brachial and carotid PP in healthy young males (Bertovic, Waddell, Gatzka et al., 1999). As the investigation was cross-sectional, discussion of potential mechanisms is difficult, however investigators suggest that the acute elevations in arterial BP may lead to long-term changes in vascular smooth muscle content and load-bearing properties of collagen and elastin, and higher sympathetic nervous system activity (Bertovic, Waddell, Gatzka et al., 1999; Miyachi, Donato, Yamamoto et al., 2003). However, the subjects in this study were healthy and young, and the risk of cardiovascular disease is greater for older individuals.

Regular resistance training is important as individuals age to help maintain functional capacity and prevent degenerative diseases (Miyachi, Donato, Yamamoto et al., 2003). Therefore Miyachi and colleagues (2003) examined the effects of resistance training on young and middle aged normotensive men. This cross-sectional study determined that central arterial compliance was 30% lower in healthy, middle-aged resistance trained men than sedentary control subjects (Miyachi, Donato, Yamamoto et al., 2003). Diffferences in arterial compliance were only found in central arteries, not the more muscular peripheral arteries, suggesting that changes may only be seen in more

elastic arteries which dampen fluctuations in pressure and flow (Miyachi, Donato, Yamamoto et al., 2003). The current data examining resistance training and arterial compliance were collected with cross-sectional investigations and need to be confirmed with future exercise intervention studies. There are also no current data on the effects of resistance training and arterial compliance in older hypertensive individuals, a group who would greatly benefit from improvements in BP and arterial compliance.

2.5.6.3 Isometric Training

There are currently no data examining the effects of isometric training on arterial compliance in healthy or hypertensive individuals. Previous investigations have found a reduction in arterial BP with isometric training (Taylor, McCartney, Kamath et al., 2003; Wiley, Dunn, Cox et al., 1992), but were not able to conclusively identify the mechanisms responsible for the change. An improvement in arterial compliance of central and peripheral arteries may be involved in the reduction in BP found with isometric training but further investigations are required.

Chapter 3. Methods

3.1 Subjects

Twenty-two medicated hypertensive individuals (13 males and 9 females) ranging in age from 40 to 82 years with an average age of 66 ± 1.7 (mean, ± SEM) participated in the investigation (Table 1). All participants had no previous experience with isometric handgrip exercise and were randomly assigned to one of the experimental groups or to the control group. Ten participants (8 males and 2 females) were assigned to the one-hand isometric training group, 7 participants (4 males and 3 females) participated in the 2-hand isometric training group and 5 participants (1 males and 4 females) did not train and served as the control group.

Participants were recruited through poster campaigns at the McMaster University Seniors' Exercise Program, McMaster University MacTurtles Cardiac Rehabilitation Program, and advertisements within McMaster University and in local newspapers and radio stations.

Participants were included if they were in good general health and medicated for hypertension. Participants were excluded if they had a history of smoking, diabetes, heart failure and/or a change in medication throughout the investigation.

The research protocol was reviewed and approved through the McMaster Medical Research Ethics Board. Prior to participating in the investigation informed written consent was obtained from all participants.

After consenting to participate in the study, all subjects were told the importance of maintaining similar eating habits, exercise levels and medications throughout the

study. All participants were screened/habituated to the laboratory setting prior to pre-testing. Initial screening required that participants visited the lab to be shown the surroundings, testing equipment and procedures and discuss their time commitment. On separate visits prior to the pre-testing and eight week testing, cholesterol values were measured from blood samples taken from the antecubital vein after an overnight fast. Total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol values were determined by the McMaster Hospital Clinical Chemistry Laboratory.

Table 3.1 Participant Characteristics

Demographics	One-hand training group	Two-hand training group	Controls
Age (years)	66.3 ± 1.9	63.1 ± 4.0	69.2 ± 2.5
Gender	8 males, 2 females	4 males, 3 females	1 male, 4 females
Height (inches)	67.4 ± 1.2	70.3 ± 2.1	64.8 ± 1.5
Weight (lbs)	173.4 ± 13.3	190.8 ± 14.6	166.2 ± 17.2
Resting SBP (mmHg)	140.1 ± 3.8	136.2 ± 5.2	134.4 ± 4.1
Resting DBP (mmHg)	78.6 ± 3.6	73.3 ± 2.9	67.2 ± 1.9
Total Cholesterol	4.6 ± 0.29	5.1 ± 0.65	5.3 ± 0.11
LDL Cholesterol	2.5 ± 0.28	2.8 ± 0.36	3.2 ± 0.19
HDL Cholesterol	1.3 ± 0.10	1.1 ± 0.066	1.5 ± 0.39
Triglycerides	1.7 ± 0.28	2.4 ± 0.58	1.6 ± 0.65
Glucose random	5.7 ± 0.21	5.5 ± 0.21	5.4 ± 0.50

3.2 Experimental Design

Isometric handgrip training was performed with a digital handgrip dynamometer (CardioGrip, MD Systems, Westerville, USA) three times a week for eight weeks. Each week participants completed two of the training sessions in the Centre for Health Promotion and Rehabilitation at McMaster University, and the third training session was

done at home. Participants were instructed to perform training sessions at the same time of day and leave at least one day of rest between training sessions. Each participant was assigned a handgrip dynamometer to train with, consistent volunteers per training session, and an exercise logbook. The digital handgrip dynamometer provided subjects with visual and auditory cues regarding timing of contractions, rest periods and the amount of force produced by each contraction. Two electronic load cells in the dynamometer recorded the amount of force produced during the contractions and displayed the amount in pounds on a display screen.

Before beginning an exercise session in the Centre, each participant's resting blood pressure was recorded after 5minutes of seated rest. Blood pressure was measured indirectly from the brachial artery with a semiautomatic blood pressure machine (Dynamap XL; Johnson and Johnson, USA) and recorded in the exercise logbook. Volunteers also recorded the activities performed on the day of training and/or stressful events that occurred previous to the training session. Activities performed between training sessions, changes in medication and/or symptoms were also entered in the logbook at each visit to the Centre.

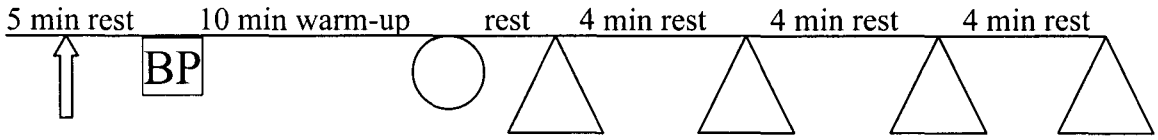
After a 5-10 minute warm-up on a treadmill or stationary cycle ergometer, participants were seated at a table in the Centre for Health Promotion and Rehabilitation to perform their isometric handgrip training. Subjects performed the training in a seated position with their elbow bent at 90°, forearm and hand resting on the table and display screen facing the participant to provide visual feedback during the training session. Once the participants were properly set up the dynamometer was turned on, and training began.

Training was completed according to the one-hand isometric training protocol (1HG) or the two-hand isometric training protocol (2HG).

3.3 Training Protocols

Each training protocol began with the measurement of a maximal contraction with either one hand (1HG) or both hands (2HG) to determine grip strength. These contractions were brief (2sec) and were used to establish 30% of the maximal voluntary contraction (MVC), as the target exercise force. The individuals in the 1HG trained only the non-dominant hand, while the individuals in the 2HG trained both the right and the left hand alternately. Each group completed four two-minute isometric contractions at 30%MVC separated by rest periods to allow for sufficient recovery time to limit ischemic pain and fatigue. The participants were prompted to contract at 30%MVC by visual and auditory signals on the handgrip. Verbal encouragement was provided by the volunteers to assist the participants in maintaining the force of the contraction for the two minutes. The amount of force produced was represented numerically from 0-100 on the screen with 100 indicating an exact production of 30%MVC. Upon completion of each contraction, the dynamometer produced a score of the participant's ability to maintain the contraction at the target force over the 2 minutes as well as a total score at the end of each training session. The protocols were modelled after two previous studies in which isometric handgrip training at submaximal levels (30%MVC) elicited reduced blood pressure responses without significantly inducing large acute increases in blood pressure (Taylor, McCartney, Kamath et al., 2003; Wiley, Dunn, Cox et al., 1992).

One Handed Isometric Training Group



Two Handed Isometric Training Group

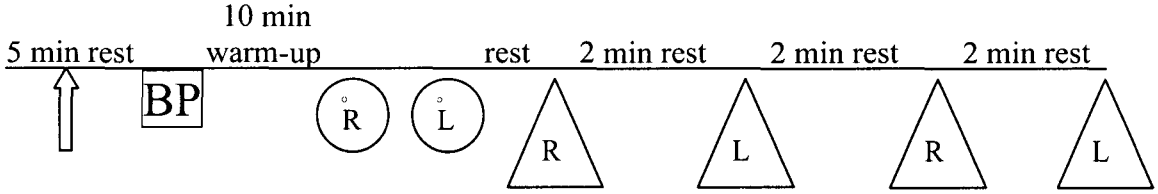


Figure 3.1: Training protocols for one-handed isometric training group and two handed isometric handgrip training group⇧ represents 5 minutes of seated rest,☐ represents seated automatic BP recording, ○ represents maximal contraction(s) and △ represents 2 minute contractions at 30%MVC.

Once a week participants were given a personalized bag with their handgrip, an instruction sheet and at-home diary to complete one session at home. Participants were instructed to complete only one training session at home and were informed that the data could be downloaded from the dynamometer to a computer to monitor their compliance.

3.4 Testing Protocol and Data Collection

Participants were instructed to abstain from caffeine and fast for at least 4 hours pre-testing, perform no vigorous exercise for 24 hours and take their medications as normal. Upon arrival in the laboratory, the participant's skin was prepared with gentle abrasion and cleaned with rubbing alcohol before the placement of 2 sets of electrodes in the modified V5 position. The electrocardiogram (ECG) signal (model Cardiomatic

MSC 7123, Medical Systems Corp, USA) was utilized to coordinate the timing for the analysis of diameters and pressures acquired over the same QRS complex.

Resting blood pressure and arterial compliance were assessed during testing sessions for all participants before training commenced, after 4 weeks of training and at the end of the 8-week training protocol. All testing was completed in a laboratory setting in the Ivor Wynne Centre at McMaster University. The testing room was kept quiet and maintained at a comfortable temperature during all testing sessions. All testing procedures followed the same sequence, and for the most part the same experienced investigator collected the imaging data and blood pressure data for each subject over the 3 testing sessions. Arterial diameters were determined using B-mode ultrasound (model System FiVe, GE Medical Systems, USA) with a hand-held 10MHz linear array probe. Continuous blood pressure measurements were acquired with an automatic inflatable oscillometric cuff positioned on the upper arm and an automated tonometer over the radial artery (model CBM-7000, Colin Medical Instruments, San Antonio, USA). Direct blood pressure measurements over the artery of interest were obtained with a hand-held pencil like tonometer probe containing a high-fidelity strain-gauge transducer (model SPT-301, Millar Instruments Inc., Texas, USA).

3.4.1 Resting Blood Pressure

Blood pressure readings were measured non-invasively according to the principle of applanation tonometry. Direct BP in the artery of interest was acquired using a pencil type probe held on the surface of the skin over the area of the vessel of interest with maximal pulsation (model SPT-301, Millar Instruments Inc., Texas, USA). The probe

was held against a rigid structure to allow for the curved surface of the artery to be flattened. Flattening of the artery balances the circumferential stress in the arterial wall, allowing the sensor to register a pressure equal to the intra-arterial pressure. Enough hold down force was used to produce a pulse pressure amplitude large enough to ensure applanation of the arterial wall. It was considered that applanation had occurred when the pressure waveforms were consistent and reproducible over several cardiac cycles. This technique is best used on more superficial arteries such as the carotid, femoral and radial, where tissue deposits do not interfere with the acquisition of optimal waveforms (Kelly, Hayward, Avolio et al., 1989). Use of the pencil type applanation tonometer allows for direct measurements of BP in the artery of interest at the site of the diameter recording. However, baseline levels are subject to hold down force and the BP signal obtained is not a calibrated signal. Therefore, simultaneous measurement of a calibrated radial artery pressure allows for calibration of the pencil type applanation tonometer signal.

The second method of BP assessment was performed using an automatic cuff positioned on the upper arm of the participant, a splint to open the wrist of the participant to expose the radial artery and an automated tonometer placed over the radial pulse (model CBM-7000, Colin Medical Instruments, San Antonio, USA). The wrist sensor was automatically adjusted to apply an appropriate hold down pressure to record a waveform with optimal signal strength. The tonometer BP recording at the wrist was then calibrated to the automated arm cuff value. The hold down pressure was continuously adjusted to equalize the intra-arterial pressure of the radial artery, thereby

providing continuous blood pressure recordings. The radial mean and diastolic blood pressure values were used to calibrate the BP signals from the pencil type tonometer used over the carotid and brachial arteries.

The analogue outputs from the radial tonometer, pencil tonometer and ECG were sampled at 200Hz through an analog-to-digital converter (model ML795, ADInstruments, Colorado Springs, USA) to allow data acquisition and subsequently stored on a personal computer (IBM Netvista x86 compatible processor, White Plains, USA) using data acquisition software (Chart 4.2, ADInstruments, Colorado Springs, USA).

Once the blood pressure and heart rate readings stabilized, participants were left for 20 minutes of quiet, supine rest in the darkened laboratory. Oscillometric BP measurements from the brachial artery were recorded at 12, 14 and 16 minutes of rest.

3.4.2 Resting Cross-Sectional Arterial Compliance

After the rest period was complete, blood pressure values were recorded in the right carotid artery with the pencil type applanation tonometer as simultaneous ultrasound images were recorded from the left carotid artery. Three clear ultrasound images were obtained ~2cm proximal to the bifurcation of the carotid artery. Ultrasound images were retrieved with the application of the least amount of pressure possible by the probe to allow for expansion of the carotid artery in all directions (Simons, Bots, Algra et al., 1998). Once the carotid images were completed, ultrasound and blood pressure measurements were acquired for the left brachial artery. Images were obtained from the brachial artery ~3-5cm proximal to the antecubital fossa and prior to bifurcation, at the same time as the direct blood pressure measurements were collected slightly distal to the

ultrasound transducer. Collection of data from the right arm required repositioning the participant 180 degrees on the bed and repositioning of the oscillometric BP cuff on the left arm. Once the BP signals restabilized, simultaneous ultrasound images and blood pressure readings were recorded for the right brachial artery as described for the left brachial artery above.

All ultrasound data were recorded on a super VHS videotape and also digitally stored for later off-line analysis.

3.5 Data Analysis

The same investigator analyzed all diameters, blood pressure measurements and performed compliance calculations for each subject.

3.5.1 Resting Arterial Blood Pressure

Blood pressure values were analyzed using Chart 4.2 software to determine pulse pressure values acquired simultaneously with each Doppler ultrasound image. For each artery image, waveforms produced by both the pencil type tonometer over the artery of interest and the radial artery tonometer were analyzed for minimum values (diastolic pressure), maximum values (systolic pressure) and mean arterial pressures. A trigger identifying timing acquisition of a digital ultrasound image allowed the investigator to analyze the corresponding waveform. An R-to-R interval was highlighted to ensure a complete waveform was analyzed.

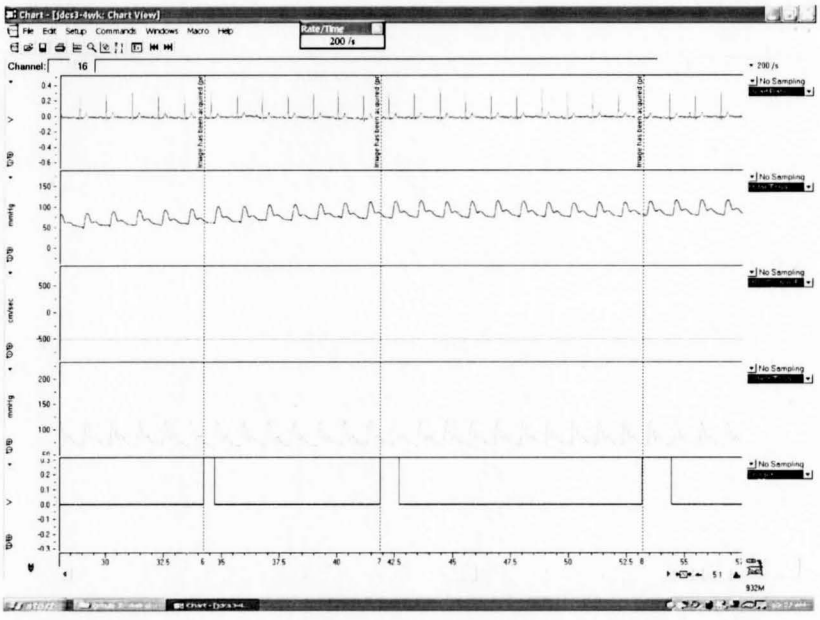


Figure 3.2 Sample of Chart 4.2 screenshot for single data recording session. Channel 1 is continuous ECG tracing, Channel 2 continuous blood pressure measurements at brachial or carotid artery, Channel 3 records mean blood velocity and Channel 4 records continuous blood pressure measurements at the radial artery. Dotted lines and bars in Channel 5 represent trigger points associated with Ultrasound digital image storage.

The pressure values obtained were exported to Excel (Microsoft Office version 2000) where the tonometer signals at the artery of interest were calibrated and pulse pressure was determined as

$$\text{Pulse Pressure} = Ds - Dd \qquad \text{(equation \#1)}$$

where, Ds = maximum (systolic) diameter
Dd = minimum (diastolic) diameter

3.5.2 Resting Arterial Diameters

Arterial diameters were measured from the ultrasound images digitally stored with Echopac Software (Echopac version 4.2, GE Medical, USA). Each digital image was transferred to a DICOM file and then analyzed by an automated edge detection system [Arterial Measurement System (AMS) II, Chalmers University of Technology, Göteborg,

Sweden]. The edge detection system permits examination of each digital image and determination of the maximum (systolic) diameter and the minimum (diastolic) diameter. The diameters were determined by analysis of a selected region of an artery, encompassing both borders of the vessel. A series of points was used by the edge detection system to detect the outer layer of the intima of the near wall and the inner layer of the intima of the far wall.

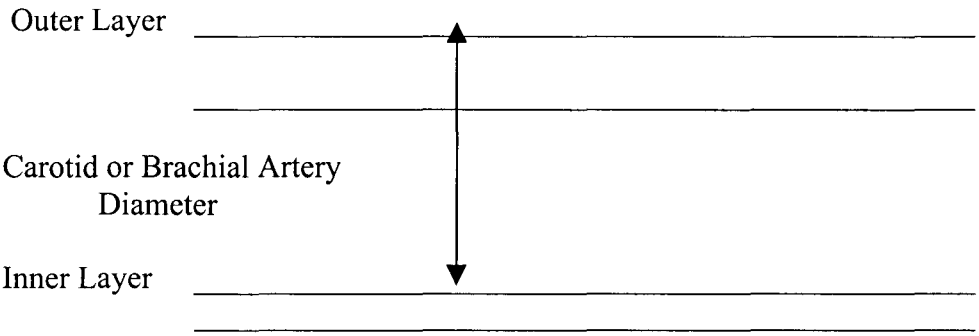


Figure 3.3: Depiction of measurement parameters for arterial diameter measurements in carotid and brachial arteries

These series of points (min. 100) were manually modified to properly identify the borders when the investigator felt the area identified by the computer was inaccurate. The amount of correction depended greatly on the quality of the image. Once all the slides for an image of an artery were analyzed, the data was saved and the lumen diameter measurements calculated by the computer software. Lumen diameter mean was measured from outer layer of the near to the inner layer of the far wall. All data were exported to Excel (Microsoft Office 2000) for further analysis.

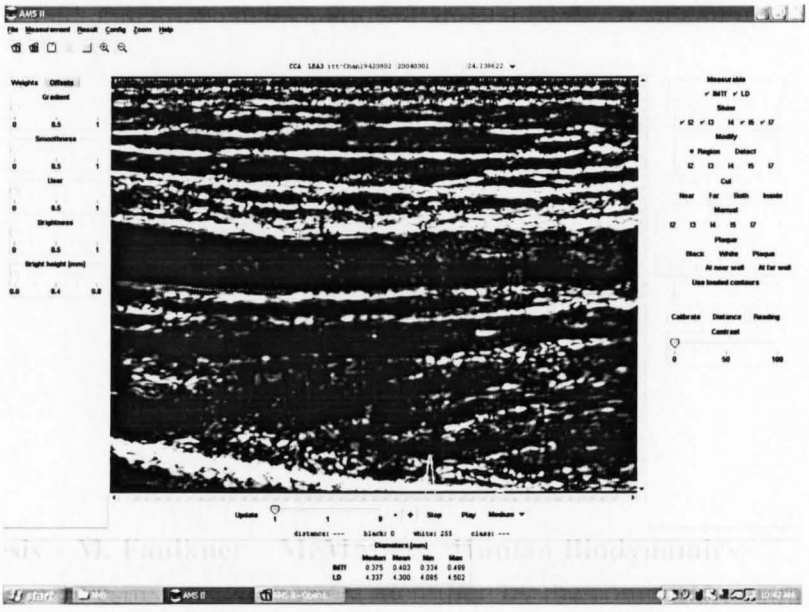


Figure 3.4: Automated edge detection system software (AMS II) screen. Area to be analyzed identified with angles and dots identify the automatically detected vessel walls.

Mean arterial diameters were estimated from the average of 2 measurements according to the following formula

$$\text{Mean arterial diameter} = Dd + \frac{(Ds-Dd)}{3} \qquad \text{(equation \#2)}$$

Dd = minimum (diastolic) diameter
Ds = maximum (systolic) diameter

The maximum and minimum arterial diameter values were also used to determine the change in diameter as

Change in diameter = Maximum diameter – Minimum diameter (equation #3)

Change in diameter values were calculated for the carotid and both brachial arteries from the maximum and minimum diameter values acquired from the automated edge-detection program.

3.5.3 Resting Cross-Sectional Arterial Compliance

Arterial compliance was determined by combining arterial ultrasound imaging with simultaneous blood pressure measurements as recommended by O'Rourke et al (2002). Arterial compliance was calculated for the carotid and brachial arteries for 2 images from the same artery and the results averaged. The formula used to determine cross-sectional compliance was (O'Rourke, Staessen, Vlachopoulos et al., 2002):

$$\text{Cross-Sectional Compliance} = \frac{\text{area}}{PP} \qquad \text{(equation \#4)}$$

$$= \frac{\pi r^2 \text{max} - \pi r^2 \text{min}}{PP}$$

$$= \frac{\pi(Dmax/2)^2 - \pi(Dmin/2)^2}{PP}$$

Where PP = pulse pressure
r = radius of the artery
Dmax = maximal diameter of the artery
Dmin = minimal diameter of the artery

The compliance was determined from the maximum and minimum radius of the artery and PP as previously described.

3.6 Statistical Analysis

All data were analyzed using a two-way analysis of variance (ANOVA) with repeated measures. Group (1HG, 2HG, control) was the first variable with time (baseline, 4-week, 8-week) as the second variable. The dependant variables included systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure, carotid arterial compliance, and brachial arterial compliance. A Tukey's Honestly Significant Difference (HSD) post hoc analysis was performed if a significant main effect was noted to

determine specific differences between the groups. Statistical significance was set at an alpha level of <0.05.

Chapter 4. Results

4.1 Resting Brachial Artery Blood Pressure

4.1.1 Systolic Blood Pressure

Statistical analysis of SBP revealed a main effect for TIME ($P<0.05$) and no effect of group. Post hoc analysis indicated that systolic blood pressure decreased significantly from pre-test to four-week ($P<0.05$) and pre-test to eight-week (Table 4.1, Figure 4.1) across all groups.

Table 4.1 Resting Systolic Blood Pressure Pre, 4-week and 8-week

	Pre	4-Week	8-Week
Control	136.5 ± 5.8	130.4 ± 5.6	131.9± 5.9
One-hand	140.1 ± 4.1	135.3 ± 4.0	132.3 ± 4.2
Two-Hand	135.7 ± 4.9	124.5 ± 4.8	124.7 ± 5.0

All values are mean ± SEM in mmHg

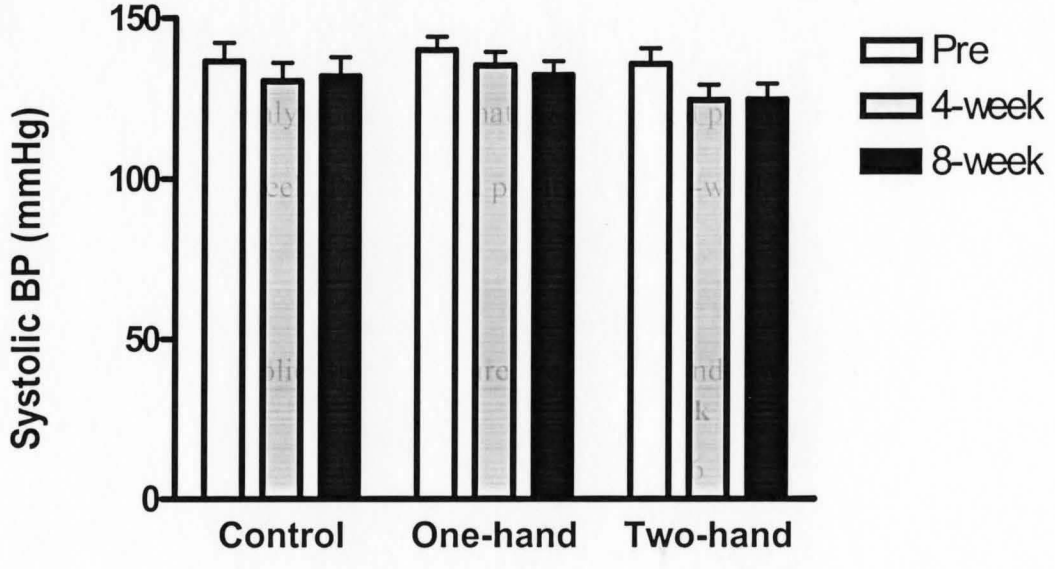


Figure 4.1 Resting Systolic Blood Pressure (SBP) at Pre, 4-week and 8-week time points

Statistical analysis revealed a main effect for TIME ($P<0.05$) and no effect for group in SBP between the exercising participants and the non-exercising control participants. Systolic blood pressure decreased significantly from pre-test to four-week ($P<0.05$) and pre-test to eight week (Table 4.2, Figure 4.2)

Table 4.2 Resting systolic blood pressure pre, 4-week and 8-week in the exercising participants versus non-exercising control participants

	Pre	4-Week	8-Week
Control participants	136.5 ± 5.7	130.4 ± 5.9	131.9 ± 5.9
Exercising participants	138.3 ± 3.1	130.9 ± 3.2	129.2 ± 3.2

All values are mean ± SEM in mmHg

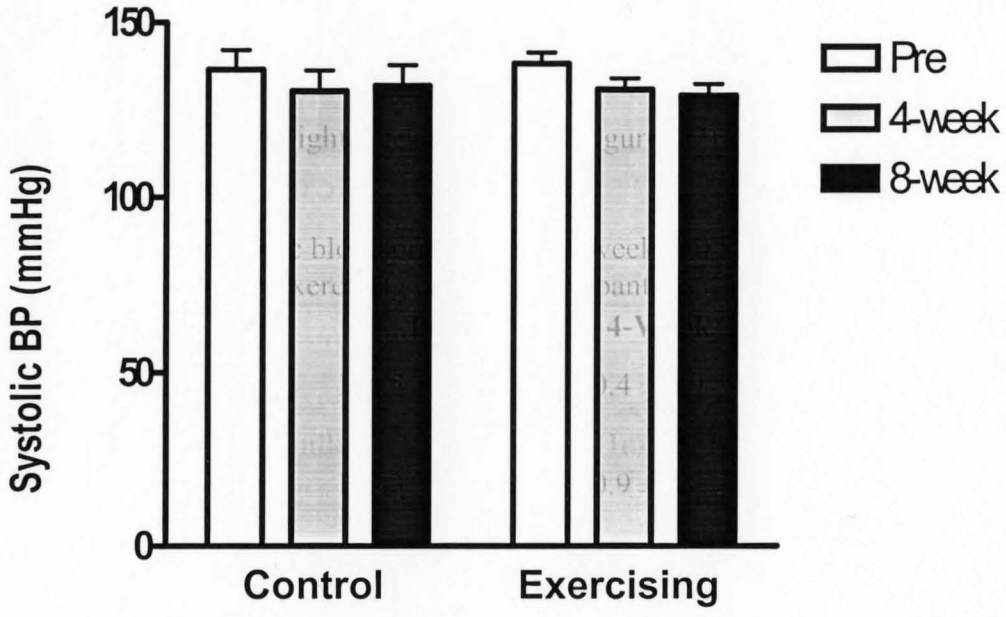


Figure 4.2 Resting Systolic Blood Pressure (SBP) in exercising participants and non-exercising controls at Pre, 4-week and 8-week time points

4.1.2 Diastolic Blood Pressure

A two-way ANOVA performed on DBP showed a main effect for GROUP ($P<0.05$) and no effect of time. A difference between control DBP and one-handed isometric training group ($p<0.05$) was found through post-hoc analysis (Table 4.3 Figure 4.3).

Table 4.3 Resting Diastolic Blood Pressure One-Hand, Two-Hand and Control

	Pre	4-week	8-week
Control	68.9 ± 4.1	64.5 ± 4.0	65.6 ± 3.7
One-hand	78.6 ± 2.9	77.5 ± 2.8	76.1 ± 2.6
Two-hand	73.0 ± 3.5	69.8 ± 3.4	69.5 ± 3.1

All values are mean ± SEM in mmHg

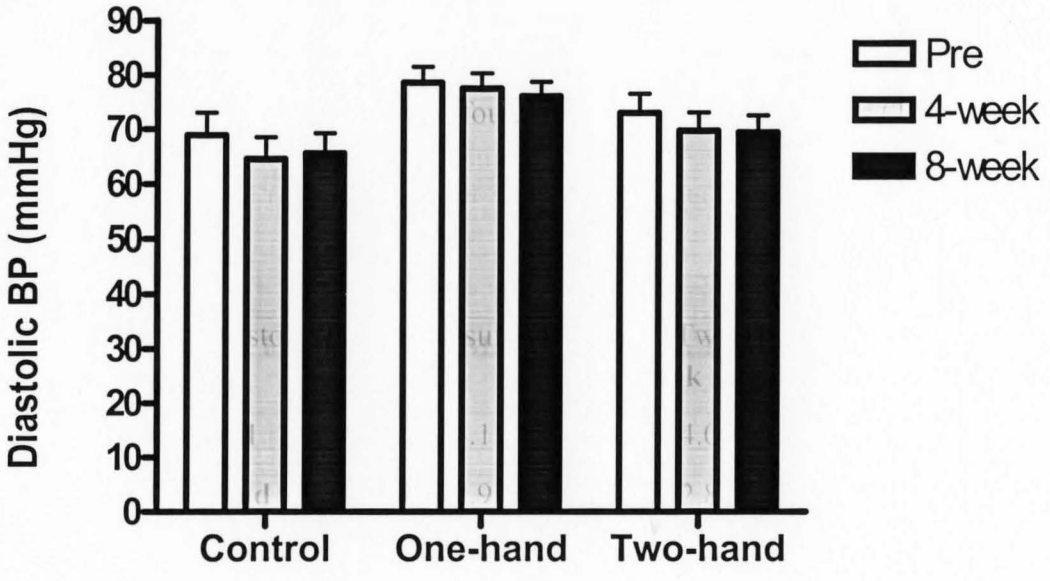


Figure 4.3 Resting Diastolic Blood Pressure One-Hand, Two-Hand and Control

Statistical analysis revealed no significant effect over time or between groups for diastolic blood pressure between exercising participants and non-exercising control participants. However, there was a trend toward significance for a main effect for group between the exercisers and the non-exercising controls (P=0.056) (Table 4.4, Figure 4.4).

Table 4.4 Resting diastolic blood pressure pre, 4-week and 8-week in the exercising participants versus non-exercising control participants

	Pre	4-Week	8-Week
Control participants	68.9 ± 4.2	64.5 ± 4.2	65.6 ± 3.8
Exercising participants	76.3 ± 2.3	74.4 ± 2.3	73.4 ± 2.1

All values are mean ± SEM in mmHg

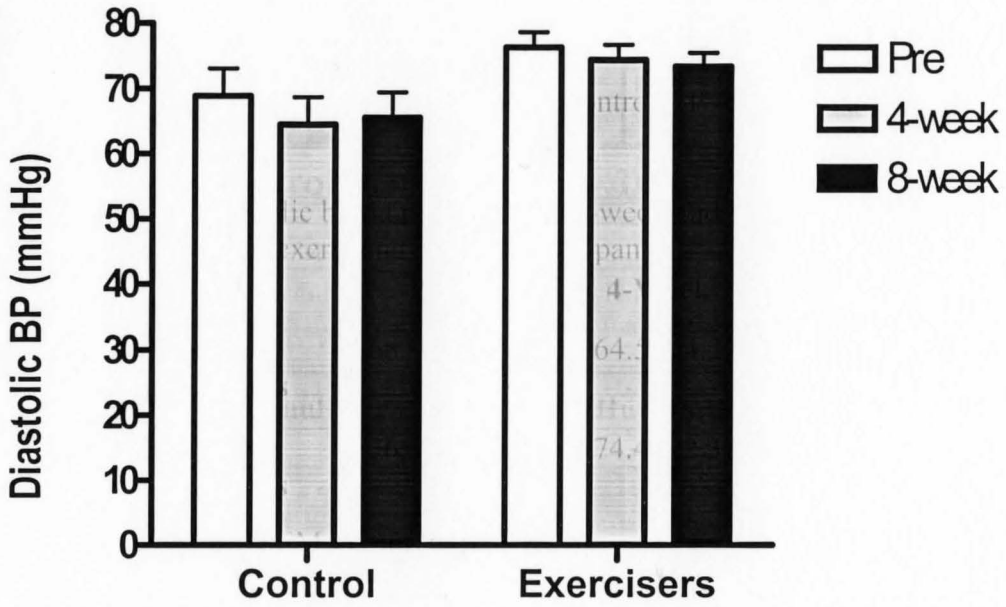


Figure 4.4 Resting Diastolic Blood Pressure exercising participants and non-exercising controls

4.1.3 Mean Arterial Pressure

Mean Arterial Pressure showed a significant effect of TIME from pre-testing to four-week ($P<0.05$) and between pre-testing and eight-week ($P<0.05$) (Table 4.5, Figure 4.5). There was no main effect of GROUP (Table 4.5, Figure 4.5).

Table 4.5 Resting Mean Arterial Blood Pressure Pre, 4-week and 8-week

	Pre	4-Week	8-Week
Control	91.4 ± 3.9	86.5 ± 4.1	87.7 ± 3.6
One-Hand	99.1 ± 2.7	96.8 ± 2.9	94.8 ± 2.6
Two-hand	93.9 ± 3.3	88.0 ± 3.5	87.9 ± 3.1

All values are mean ± SEM in mmHg

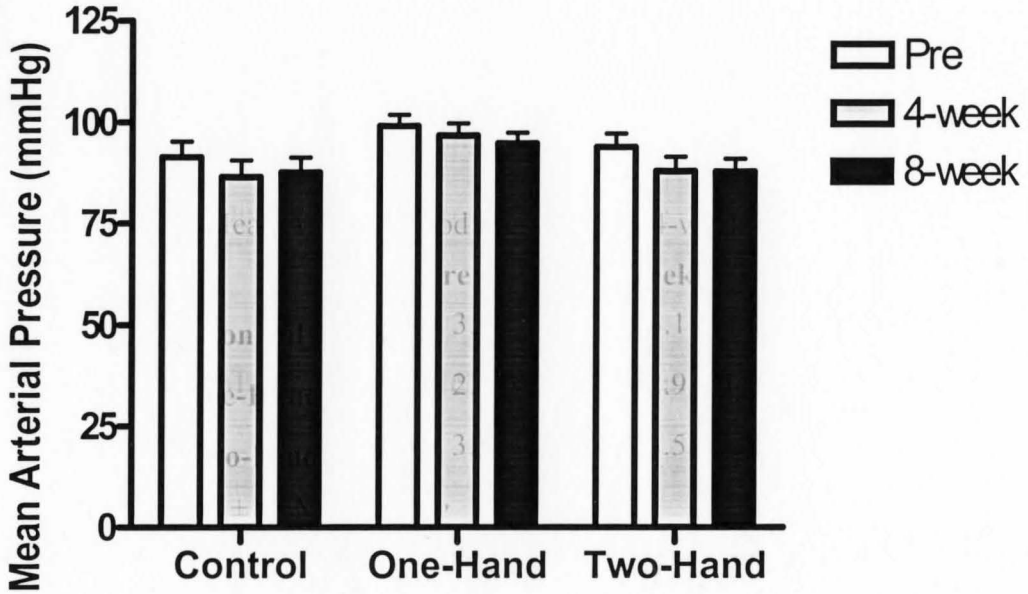


Figure 4.5 Resting Mean Arterial Pressure at Pre, 4-week and 8-week

A two-way ANOVA revealed a main effect for TIME ($P<0.05$) and no effect for group for MAP between exercising participants and non-exercising control participants. MAP was significantly different from pre-testing to four-week ($P<0.05$) and between pre-testing and eight-week ($P<0.05$) (Table 4.6, Figure 4.6).

Table 4.6 Resting Mean Arterial Pressure pre, 4-week and 8-week in the exercising participants versus non-exercising control participants

	Pre	**4-Week**	**8-Week**
Control participants	91.4 ± 3.9	86.5 ± 4.4	87.7 ± 3.8
Exercising participants	96.9 ± 2.1	93.2 ± 2.4	92.0 ± 2.1

All values are mean ± SEM in mmHg

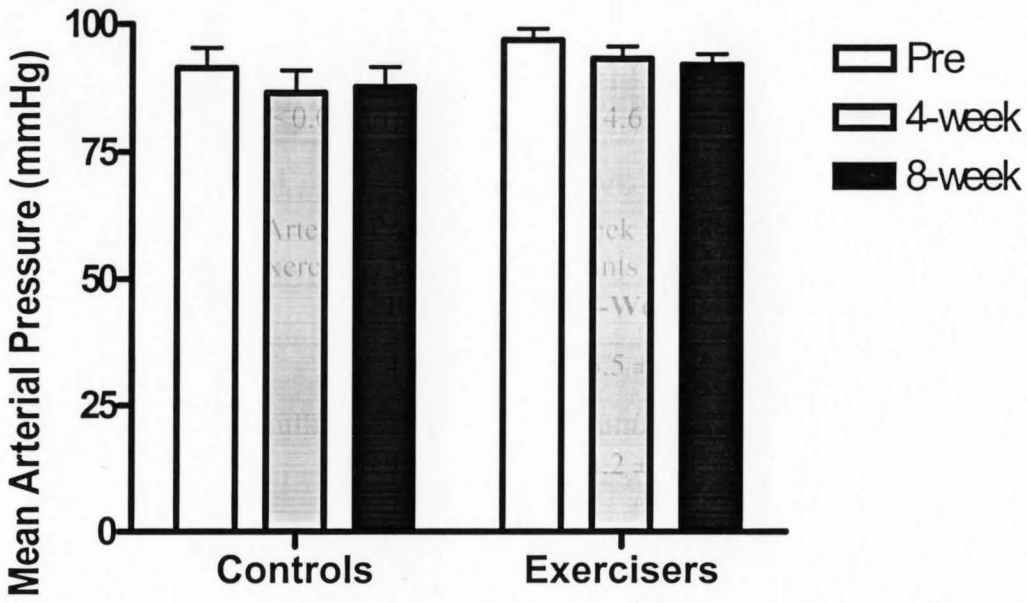


Figure 4.6 Resting Mean Arterial Pressure in the exercising participants versus non-exercising control participants

4.1.4 Brachial Artery Pulse Pressure

Statistical analysis of brachial artery pulse pressure with a two-way ANOVA revealed a main effect for TIME ($P<0.05$) and no effect for group. Pulse pressure was significantly different from pre-testing to four-week ($P<0.05$) and between pre-testing and eight-week testing ($P<0.05$) (Table 4.7, Figure 4.7).

Table 4.7 Resting Pulse Pressure Pre, 4-week and 8-week

	Pre	4-Week	8-Week
Control	67.7 ± 5.8	65.9 ± 4.5	66.3 ± 5.8
One-hand	61.5 ± 4.1	57.8 ± 3.2	56.2 ± 4.1
Two-hand	62.7 ± 4.9	54.7 ± 3.8	55.2 ± 4.9

All values are mean ± SEM in mmHg

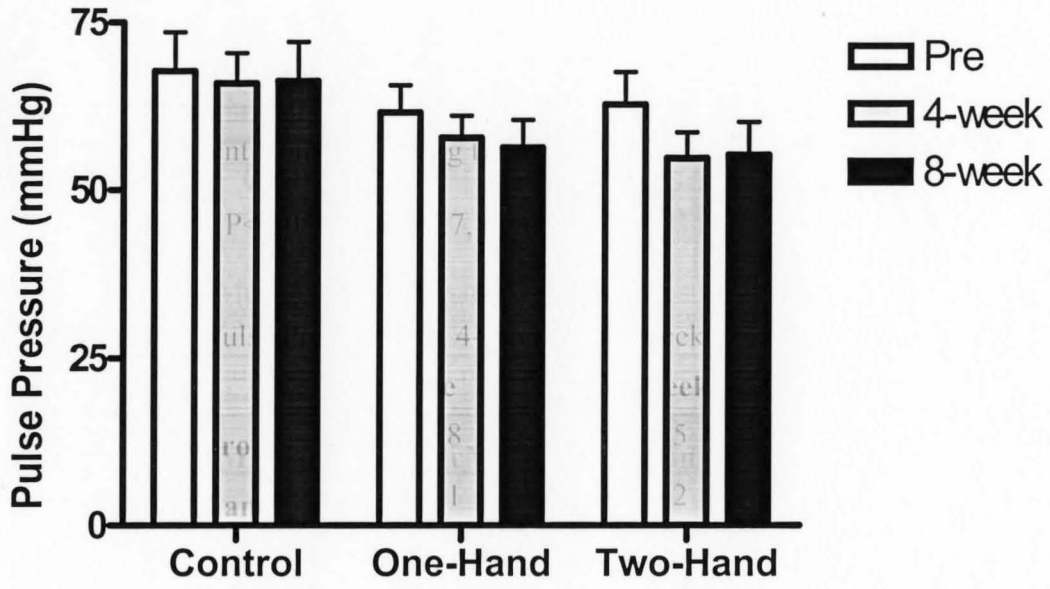


Figure 4.7 Resting Pulse Pressure at Pre, 4-week and 8-week

Statistical analysis revealed no effect over time or between groups ($P>0.05$) for brachial artery PP in the exercising participants and the non-exercising controls (Table 4.8).

Table 4.8 Resting Pulse Pressure pre, 4-week and 8-week in the exercising participants versus non-exercising control participants

	Pre	**4-Week**	**8-Week**
Control participants	67.7 ± 5.7	65.9 ± 4.4	66.3 ± 5.6
Exercising participants	62.0 ± 3.1	56.5 ± 2.4	55.8 ± 3.1

All values are mean ± SEM in mmHg

4.2 Resting Arterial Diameters

4.2.1 Brachial Artery Diameters

There were no effects for time or group in brachial arterial diameter ($p>0.05$) of the exercising arm in the 1-hand IHG as compared to the 2-hand IHG and non-exercising arms of the control group at any time point throughout the investigation (Table 4.9).

Table 4.9 Brachial arterial diameter pre, 4-week and 8-week training in the 1-hand IHG, 2-hand IHG and Control groups

	Pre	4-week	8-week
1-Hand IHG	4.05 ± 0.29	4.15 ± 0.26	3.87 ± 0.26
2-Hand IHG	4.01 ± 0.25	4.19 ± 0.23	4.29 ± 0.23
Control Group	3.93 ± 0.28	4.02 ± 0.25	4.07 ± 0.25

All values are displayed as mean ± SEM in mm

No effects for time or group were found in the brachial arterial diameter of the exercising arms as compared to the arterial diameter of the brachial arteries in the control group's arms at any time point (Table 4.10).

Table 4.10 Brachial arterial diameter in the exercising arms versus the control arms pre, 4-week and 8-week.

	Pre	4-week	8-week
Exercising arms	4.03 ± 0.19	4.18 ± 0.17	4.11 ± 0.18
Control arms	3.93 ± 0.27	4.02 ± 0.25	4.07 ± 0.26

All values are displayed as mean ± SEM in mm

There was no effect of time or group on the diameter of the brachial artery in the non-exercising arm of the one-hand isometric training group versus the control group's brachial artery at pre, 4-week or 8-week testing (Table 4.11)

Table 4.11 Brachial artery diameter in the non-exercising arm of the 1-hand IHG group versus the control arms pre, 4-week and 8-week.

	Pre	**4-week**	**8-week**
1-hand IHG non exercising arm	4.18 ± 0.33	4.33 ± 0.29	4.37 ± 0.30
Control arms	3.93 ± 0.27	4.02 ± 0.24	4.07 ± 0.25

All values are displayed as mean ± SEM in mm

4.2.2 Carotid Arterial Diameters

There were no effects for time or group in carotid artery diameters between the 1-hand IHG, 2-hand IHG and control group at pre, 4-week and 8-week testing (Table 4.12)

Table 4.12 Carotid artery diameter pre, 4-week and 8-week training in the 1-hand IHG, 2-hand IHG and Control groups

	Pre	4-week	8-week
1-Hand IHG	6.60 ± 0.44	6.95 ± 0.27	6.75 ± 0.29
2-Hand IHG	7.21 ± 0.53	6.95 ± 0.33	7.14 ± 0.36
Control Group	6.61 ± 0.59	6.90 ± 0.36	6.83 ± 0.40

All values are displayed as mean ± SEM in mm

There were no effects for time or group in the carotid artery diameter of the exercising participants as compared to the non-exercising controls at any time point throughout the training (Table 4.13).

Table 4.13 Carotid artery diameter in the exercising group versus the control group pre, 4-week and 8-week training.

	Pre	4-week	8-week
Exercising group	6.84 ± 0.34	6.95 ± 0.20	6.91 ± 0.22
Control group	6.61 ± 0.58	6.90 ± 0.35	6.83 ± 0.39

All values are displayed as mean ± SEM in mm

4.3 Resting Arterial Cross-Sectional Compliance

4.3.1 Brachial Artery Cross-Sectional Compliance

There was no effect over time or between groups in brachial artery cross-sectional compliance (CSC) ($P>0.05$) of the exercising arm in the 1-hand IHG as compared to the 2-hand IHG and control group (Table 4.14).

Table 4.14 Brachial artery cross-sectional compliance (CSC) pre, 4-week and 8-week training in the 1-hand IHG, 2-hand IHG and Control groups

	Pre	4-week	8-week
Control	0.019 ± 0.003	0.024 ± 0.003	0.027 ± 0.005
One-hand	0.021 ± 0.004	0.019 ± 0.003	0.023 ± 0.005
Two-hand	0.026 ± 0.003	0.026 ± 0.003	0.029 ± 0.004

All values are displayed as mean ± SEM in $mm^2/mmHg$

There were no differences between groups or over time in the brachial artery CSC of the exercising arms as compared to the arterial compliance of the brachial arteries in the control group's arms (Table 4.15).

Table 4.15 Brachial artery cross-sectional compliance (CSC) in the exercising arms versus the control arms pre, 4-week and 8-week.

	Pre	4-week	8-week
Exercising arm	0.024 ± 0.002	0.023 ± 0.002	0.026 ± 0.003
Control arms	0.019 ± 0.003	0.024 ± 0.003	0.027 ± 0.005

All values are displayed as mean ± SEM in $mm^2/mmHg$

One-hand isometric hand-grip training did not induce significant changes ($p>0.05$) in CSC of the brachial artery in the non-exercising arm versus the control group's arms over time or between groups at pre, 4-week or 8-week testing (Table 4.16)

Table 4.16 Brachial artery cross-sectional (CSC) in the non-exercising arm of the 1-hand IHG group versus the control arms pre, 4-week and 8-week.

	Pre	**4-week**	**8-week**
1-hand IHG non exercising arm	0.030 ± 0.004	0.023 ± 0.004	0.027 ± 0.004
Control arms	0.019 ± 0.003	0.024 ± 0.004	0.027 ± 0.004

All values are displayed as mean ± SEM in $mm^2/mmHg$

4.3.2 Carotid Artery Cross-Sectional Compliance

There was no main effect for group for carotid artery cross-sectional compliance, however there was a trend toward significance between the 1-hand IHG and 2-hand IHG at all time points (Table 4.17, Figure 4.8). There were no significant differences between pre, 4-week and 8-week testing (Table 4.17)

Table 4.17 Carotid artery cross-sectional compliance pre, 4-week and 8-week training in the 1-IHG, 2-IHG and Control groups

	Pre	4-week	8-week
Control	0.107 ± 0.014	0.107 ± 0.015	0.113 ± 0.024
One-hand	0.105 ± 0.010	0.104 ± 0.011	0.113 ± 0.018
Two-hand	0.134 ± 0.013	0.146 ± 0.014	0.176 ± 0.022

All values are displayed as mean ± SEM in $mm^2/mmHg$

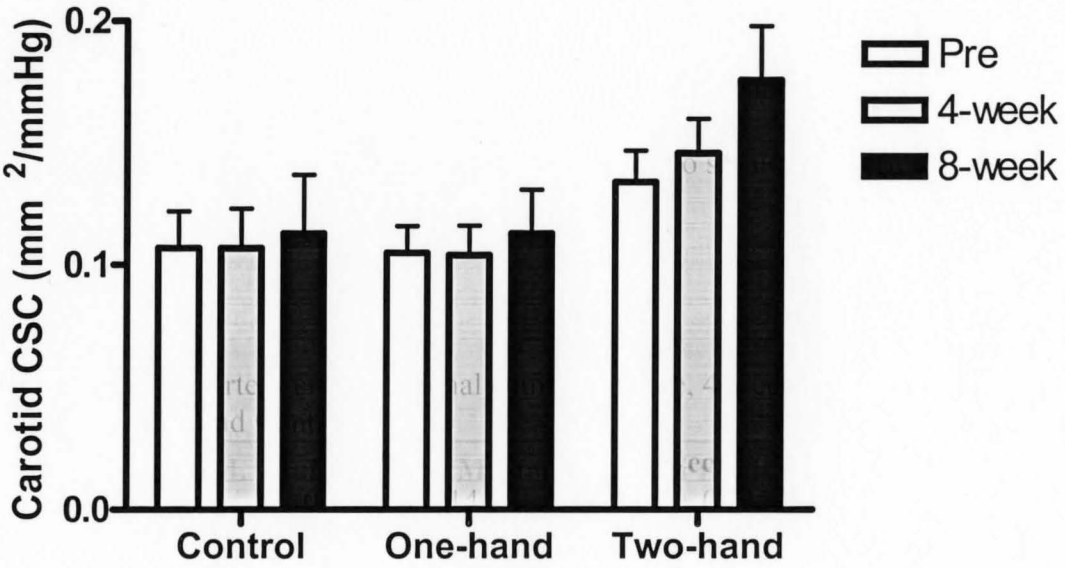


Figure 4.8 Carotid artery cross sectional compliance (CSC) for One-Hand, Two-Hand and Control groups

There were no significant differences ($p>0.05$) in carotid artery CSC of the exercising participants as compared to the non-exercising control participants over time or between groups (Table 4.18).

Table 4.18 Carotid artery cross-sectional compliance (CSC) in the exercising participants versus the non-exercising controls pre, 4-week and 8-week training.

	Pre	**4-week**	**8-week**
Exercising participants	0.117 ± 0.008	0.121 ± 0.010	0.138 ± 0.016
Control participants	0.107 ± 0.015	0.107 ± 0.017	0.113 ± 0.027

All values are displayed as mean ± SEM in $mm^2/mmHg$

Chapter 5. Discussion

The purpose of this study was to 1) determine if one-hand isometric exercise would elicit similar resting blood pressure reductions and increases in vascular compliance as two-handed isometric exercise in medicated hypertensive individuals and 2) to determine if isometric handgrip exercise would alter vascular compliance in the conduit artery directly supplying the exercising arm and/or the non-exercising muscular and elastic arteries in medicated hypertensive individuals.

5.1 Isometric training and resting blood pressure

Significant decreases in SBP, MAP, and PP were observed in the 1-IHG, 2-IHG and the control group after eight weeks of isometric training. The reductions in SBP, MAP and PP were observed between pre and 4-week as well as pre and 8-week. Main effects for time for SBP and MAP were also found in a two-way ANOVA comparing the exercising participants and the control participants. Diastolic blood pressure was not altered over time, but was significantly different between the 1-IHG and control groups at all time points. The difference in DBP between groups is important because it reflects an intrinsic disparity between participants in these groups making it difficult to compare their results. Combined these results do not support the hypothesis that 1-IHG training results in changes in ABP as changes were apparent in all groups including the controls. These results do not however eliminate the possibility that 1-IHG training contributed to the changes observed in the exercising groups.

A meta-analysis by Kelley and Kelley (2000) reported the benefits of resistance training in reducing high blood pressure. However, the blood pressure change in the

control groups was not different than the change in the resistance training groups (Wallace, 2003). Previous investigations found that a hypotensive effect could be elicited in hypertensive individuals (Taylor, McCartney, Kamath et al., 2003) and persons with high normal blood pressure (Ray & Carrasco, 2000; Wiley, Dunn, Cox et al., 1992) using repeated submaximal isometric contractions. In contrast, Somers and colleagues (1992) did not find an attenuation of blood pressure after 6 weeks of isometric handgrip training. Our study confirms these results. The absence of an attenuation of resting ABP may be due to the lack of significant changes in arterial compliance after the isometric training.

5.2 Isometric training and arterial compliance

There were no significant changes in brachial or carotid arterial compliance with isometric handgrip training. There was a trend toward significance for a main effect of time across all groups. There was also a trend toward significance between groups in carotid CSC between the 1-IHG and 2-IHG. This was the first study to examine the effects of isometric training on arterial compliance that we are aware of. Previous investigations have found an improvement in the central arterial compliance after aerobic training in the elastic carotid artery (Monahan, Dinenno, Seals et al., 2001; Tanaka, Dinenno, Monahan et al., 2000). In contrast, investigations into the effects of resistance training on arterial compliance have found lower carotid arterial compliance (Miyachi, Donato, Yamamoto et al., 2003) and whole body compliance (Bertovic, Waddell, Gatzka et al., 1999) in young and middle aged healthy men. Unfortunately the modes of training were different from the current investigation making it difficult to directly compare the results. Measurements were made in the non-exercising arm and in the exercising arm to

determine whether the effects of isometric training were localized to the exercise trained limb or were more systemic in nature. Previous work has found that four weeks of unilateral handgrip exercises did not affect vasodilatory function in the contralateral forearm (Sinoway, Shenberger, Wilson et al., 1987). The results of the current study were not significantly different between the exercising and non-exercising arms. The lack of improvement in arterial compliance in this investigation may be due to a lack of structural changes of arterial walls and/or alterations in sympathetic nerve activity or limitations in the study design.

Arterial compliance is primarily determined by the composition of elastin and collagen and the tone exerted by the vascular smooth muscle cells in the arterial wall (Tanaka, Dinenno, Monahan et al., 2000). Hypertension and ageing are associated with growth of both vascular smooth muscle and connective tissue. Changes in collagen and elastin composition are believed to occur over a period of years (Tanaka, Dinenno, Monahan et al., 2000), therefore it is unlikely that an eight-week training study could alter arterial compliance this way. The pressure load exerted by a 30% MVC contraction may not have been sufficiently large enough to induce mechanical distension and stretching of the collagen fibers to modify the cross-linking and improve arterial compliance.

An increase in sympathetic tone in vascular smooth muscle may have occurred due to higher sympathetic nervous system activity. Boutouyrie and colleagues (1994) found that sympathetic activation is able to decrease radial arterial compliance in healthy subjects. It was proposed that an increase in arterial smooth muscle tone contributed to the reduced compliance. Although compliance was not significantly improved in the

current study, we did not see a reduction in compliance either. However we cannot exclude the possibility that increased sympathetic tone contributed to the lack of improvement in arterial compliance in the current study. An increase in sympathetic tone would affect vessels all over the body; and since there was no improvement in the carotid or brachial arteries an increase in sympathetic activity could be a viable contributor to our lack of significant improvements. However an increase in sympathetic tone was unlikely, as it does not match previous research and our current observations of reduced ABP, across all groups.

5.3 Limitations

One of the major limitations of the current study was the small control group. There was a large amount of variability in the control group because of its small size (n=5). This variability may have limited our ability to find statistically significant differences between the experimental groups over time. A larger control group may reduce this variability allow the impact of the exercise training to be more apparent. The inclusion of more control subjects is currently being performed which will hopefully remove the variability and give more strength to the results.

The lack of similarity between groups also limited the results of this study. A main effect for group was found in statistical analysis of DBP and MAP at all time points. Therefore comparisons were being made across groups that were intrinsically different, and changes due to training would be difficult to find due to these differences. Larger group sizes may help to reduce this discrepancy as well as stratification to groups based on ABP or vascular characteristics. The differences in DBP between groups may not

have influenced the conclusions concerning the alterations in resting arterial blood pressure with handgrip training. Resting SBP and DBP indicate that participants in this study could be classified as having isolated systolic hypertension as their resting SBP values were somewhat high (>135mmHg) and their DBP was low (<80mmHg). This would indicate that in these participants, alterations in SBP over time would likely be more important to risk reduction than changes in DBP. However intrinsic differences in DBP between groups would influence the calculations for resting arterial compliance. Arterial compliance is calculated as the difference between SBP and DBP, therefore comparisons made across intrinsically different groups would reduce the chances of finding a significant effect.

Improvements in resting ABP and alterations in arterial compliance may not have been significant, due to limitations with measurement techniques, the population studied, the exercise-training stimulus, and/or amount of time for adaptations to occur. Timing of the ABP testing measurements after the last training session may have affected the results. Martel and colleagues (1999) found that ABP's recorded 72 hours after the last training session were not significantly different from those before training, however measurements taken within the first 48 hours after training were significantly lower. Therefore, changes in ABP may not have been consistent between individuals tested in the current study if some were tested within the 48 hours and others more than 72 hours after their last training session. It is important to remember that although reduction of ABP has been a major focus for the treatment of a high-risk population, ABP is only one of a number of factors that contribute to vascular events (Cohn, 1999). Therefore smaller

reductions in ABP and limited effects on vascular disease may occur with interventions that do not target coexistent risk factors in hypertensive individuals.

Blood pressure is very variable throughout the day and from day to day. One-time ABP recordings were utilized, however this may have been a limiting factor as ABP oscillates throughout the day. Ambulatory ABP monitoring may provide additional information when analyzing the ABP response to exercise (Wallace, 2003) in more natural, everyday settings and situations over a longer period of time.

An attempt was made to collect ABP recordings with the same equipment throughout the investigation, however due to technical difficulties certain testing sessions utilized limited ABP equipment. Lack of continuous ABP recordings due to the absence of the automated tonometer over the radial artery required investigators to use cuff measurements, while problems with the hand held tonometer did not allow for direct ABP measurements over the artery of interest. Both of these situations reduced the sensitivity of the ABP recordings which may have resulted in less accurate ABP measurements. Measurements of arterial compliance required the measurement of arterial diameter changes and simultaneous measurement of ABP. The images were sometimes difficult to obtain in obese individuals. Images from previous testing procedures were used in an attempt to image the same section of the artery at each testing session, however this was not exact and may have left room for error and therefore less precise measurements.

The age of the participants may have influenced the results. Investigations into the effects of age on the effects of exercise training on blood pressure have demonstrated that exercise-induced blood pressure reduction was greater in younger individuals (30-49

year olds) than in participants 50-69 years old, suggesting that age is an important consideration when looking at the effects of exercise on ABP (Ishikawa, Ohta, Zhang et al., 1999). Differences in vascular aging or atherosclerosis progression may explain the variability in BP reduction and arterial compliance with age. As individuals age, their arteries become stiffer and less responsive to changes in pressure (Dart, Gatzka, Cameron et al., 2004; Joyner, 2000). Progression of atherosclerosis also increases arterial stiffness; therefore an older individual with atherosclerosis may require more training than a younger individual or someone with less atherosclerosis to improve arterial compliance and ABP. Women with hypertension appear to show larger reductions in BP more often than men as a result of aerobic exercise training (Hagberg, Park, & Brown, 2000). The average SBP reduction after aerobic exercise training in women with hypertension was 14.7mmHg while hypertensive men reported average reductions of 8.7 mmHg (Hagberg, Park, & Brown, 2000). Although unclear, the difference in SBP reduction between men and women could be due to higher levels of estrogen in women or perhaps better compliance with the training protocol. The current study had nine women in total, four of whom were in the control group. The ABP reduction in the current study may have been larger had there been a larger number of women involved in the training groups.

Information related to history of blood pressure medication use, and level of physical activity were not collected for participants in the investigation and may have been confounding factors affecting the results, however baseline levels of medication and exercise were maintained throughout the study. Individuals with a longer history of hypertension may have stiffer arteries (Dart & Kingwell, 2001; Weinberger, Fineberg, &

Fineberg, 2002b), while individuals on certain medications (calcium channel blockers, ACE inhibitors, nitrates etc.) may have already maximally improved their arterial compliance (Resnick & Lester, 2002).

Dietary habits were not monitored throughout the study. An attempt was made to keep the meals prior to testing consistent, however there were no control measures in place to ensure consistency occurred. Eating a higher fat meal prior to testing may have altered arterial compliance and provided inconsistent results. Subjects with high blood glucose values have less compliant blood vessels than those with normal blood glucose values (Benetos, Waeber, Izzo et al., 2002). None of the subjects were diagnosed diabetics and their fasting blood glucose levels were below the acceptable limit of 7mmol/L (see Appendix A), however data were missing from 30% (n=7) of the participants and may have been higher than normal contributing to stiffer arteries and made them less responsive to the exercise intervention.

Reductions in BP have been found more consistently when resistance-training programmes were combined with cardiorespiratory endurance exercise than resistance training alone (Wallace, 2003). Improvements in arterial compliance have been found in aerobic training studies (Monahan, Dinenno, Seals et al., 2001; Tanaka, Dinenno, Monahan et al., 2000), but not resistance training (Bertovic, Waddell, Gatzka et al., 1999; Miyachi, Donato, Yamamoto et al., 2003). Some of the participants in this investigation were members of the MacTurtles and MacSeniors exercise program while others were members of the general public. The members of the MacTurtles and MacSeniors participate in aerobic and resistance training approximately twice a week. The

individuals from the general public may not have completed the same level of cardiorespiratory training, putting them at a deficit for ABP and vascular adaptations. Participants were asked to maintain their current lifestyle to attempt to account for this, however measurement of VO_2max before and after training could have accounted for these discrepancies and given more information into whether or not participants underwent some form of aerobic training that may have contributed to the alterations in BP. A crossover study by Jennings and colleagues (1991) determined that levels of background activity greatly affected the effect of exercise training on alterations in BP. Exercise training had a greater effect on ABP reductions during the winter months when background activity levels were lower and less of an effect in the summer when activity levels were high (Jennings, Deakin, Korner et al., 1991). These conclusions suggest that members of the MacTurtles and MacSeniors may have already maximally improved their blood pressure and arterial compliance due to their higher levels of cardiorespiratory training and therefore not responded to the isometric handgrip training as expected.

The training stimulus of 30% MVC, three times a week may not have been large enough to induce the changes required for improvements in arterial compliance. An eight-week training program may not have been long enough to induce structural changes in the carotid and brachial arteries. The length of training was chosen based on previous work examining alterations in ABP (Taylor, McCartney, Kamath et al., 2003; Wiley, Dunn, Cox et al., 1992) and may have needed to be longer to induce alterations required for improvements in arterial compliance. Alterations in arterial compliance with aerobic exercise were found after 12 (Tanaka, Dinenno, Monahan et al., 2000) and 13 weeks

(Monahan, Dinenno, Seals et al., 2001) of training. Therefore changes in arterial compliance may require a longer training period than is required to induce alterations in ABP. Muscular arteries do not exhibit age-related changes in arterial compliance, a process that occurs over years affecting the more elastic central arteries. Therefore it is difficult to expect to see changes in the muscular arteries with a short eight-week training program. In contrast alterations in central arteries (e.g. carotid) may be possible.

5.4 Future Directions

Future directions for investigations could include training protocols with different training intensities, greater duration, examination of different populations such as non-medicated hypertensives or younger at risk individuals. Examination of central arterial compliance via the aorta may also provide more direct measurements and allow a better understanding into the mechanisms behind the reductions in BP.

It is possible that different frequencies and durations may be suited to different subgroups of hypertensive patients (Wallace, 2003). Some people may not respond to exercise training as well as others, therefore their exercise prescription may be different than for those who respond more. Hypertensive individuals with the greatest risk have the greatest risk reductions with exercise training (Hagberg, Park, & Brown, 2000), therefore a more frequent and longer intervention may be required to elicit improvements in more controlled hypertensive individuals.

To examine the independent effects of training on resting BP, future studies should examine participants not on antihypertensive medication (Kelley & Kelley, 2000). The reductions in BP in hypertensive individuals on beta-blockers may be limited when

compared to individuals on other anti-hypertensive medications (Wallace, 2003). However the actions of antihypertensive medication do not seem to amplify the effects of exercise training (Wallace, 2003), suggesting taking individuals off medication for the purpose of a study may not be required. Calcium channel blockers, ACE inhibitors, nitrates and angiotensin II receptor antagonists have been found to significantly improve arterial compliance (Benetos, Laurent, Asmar et al., 1997a; Resnick & Lester, 2002). Therefore participants on these medications may have already improved their compliance as much as possible by being on the medications and not benefited further from exercise training.

Development of hypertension may be a result of loss of compliance in the aorta; therefore an improvement in aortic compliance is an important factor to examine when looking at reductions in BP and improvements in arterial compliance. Future investigations should examine central pulse pressure more directly as arterial stiffness estimated at the brachial artery often overestimates central PP (Liao, Arnett, Tyroler et al., 1999). Brachial artery tracings may also give falsely high SBP readings and falsely low DBP readings when compared with the ascending aorta (Safar & Laurent, 2003). Important pathophysiological consequences such as cardiac hypertrophy and function and cardiac perfusion are related to central pressure, therefore it is important to measure BP and arterial compliance in the central arteries (Dart & Kingwell, 2001). The carotid artery can by used to measure central pressure, however measurements of aortic pressure and compliance would provide more precise and accurate values.

The peripheral arteries such as the brachial and radial are muscular arteries, which are not representative of the more proximal elastic arteries. The changes in BP and arterial compliance are expected to be related more to changes in central arteries as these are the elastic arteries. Future investigations should therefore focus on the central arteries and set aside investigations of the muscular, peripheral arteries for the time being. Future research should also examine alternative mechanisms that contribute to the reductions in blood pressure with isometric training found in this and other studies (Taylor, McCartney, Kamath et al., 2003; Wiley, Dunn, Cox et al., 1992). Alterations in sympathetic nerve activity could be examined with measurements of muscle sympathetic nerve activity (MSNA), plasma norepinephrine levels and/or plasma angiotensin I and II. The structural composition of arteries could also be examined to assess the collagen, elastin and smooth muscle cell content, however this is very difficult in vivo and may need to be performed on animals.

5.5 Summary

This study examined the relationship between isometric training and alterations in ABP and arterial compliance in medicated hypertensive individuals. We found significant changes in resting arterial blood pressure and central and peripheral arterial compliance following eight weeks of training across all groups (1-IHG, 2-IHG and controls), therefore we are not able to conclude that the training caused the changes. These findings suggest that future studies need to be performed to assess the effects of isometric handgrip training on resting arterial blood pressure and arterial compliance with a larger subject pool.

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APPENDIX A
ANOVA Tables

Blood Pressure

Systolic Blood Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	2	355	19	387	0.919	0.416038
Time (T)	2	390	38	56	7.017	0.002550
T x G	4	31	38	56	1.030	0.403828

Systolic Blood Pressure – exercising participants and non-exercising controls

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	0.3	20	402.9	0.001	0.979211
Time (T)	2	239.8	40	55.0	4.362	0.019329
T x G	2	19.9	40	55.0	0.362	0.698459

Diastolic Blood Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	2	674.6	19	176.8	3.816	0.040430
Time (T)	2	60.0	38	27.7	2.162	0.129029
T x G	4	5.7	38	27.7	0.204	0.934619

Diastolic Blood Pressure – exercising participants and non-exercising controls

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	804.9	20	195.1	4.125	0.055768
Time (T)	2	49.7	40	26.6	1.869	0.167575
T x G	2	6.5	40	26.6	0.245	0.783498

Mean Arterial Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	2	474.1	19	165.5	2.864	0.081792
Time (T)	2	138.0	38	29.1	4.741	0.014521
T x G	4	9.4	38	29.1	0.323	0.860973

Mean Arterial Pressure – exercising participants and non-exercising controls

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	351.1	20	187.1	1.876	0.185922
Time (T)	2	97.2	40	28.3	3.433	0.042060
T x G	2	5.6	40	28.3	0.198	0.821201

Pulse Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	2	423.1	19	365.5	1.1578	0.335383
Time (T)	2	144.3	38	35.7	4.0484	0.025477
T x G	4	21.5	38	35.7	0.6026	0.663123

Pulse Pressure – exercising participants and non-exercising controls

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	835.3	20	347.8	2.4019	0.136869
Time (T)	2	71.2	40	34.8	2.0466	0.142488
T x G	2	24.2	40	34.8	0.6958	0.504616

Resting Arterial Diameters

One-hand vs. Two-hand vs. Control

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	2	0.240	28	1.873	0.1280	0.880394
Time (T)	2	0.121	56	0.082	1.4856	0.235143
T x G	4	0.166	56	0.082	2.0392	0.101251

Exercising arm vs control

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	0.175	29	1.819	0.0964	0.758471
Time (T)	2	0.121	58	0.090	1.3563	0.265650
T x G	2	0.022	58	0.090	0.2476	0.781467

Non-exercising arm vs. control

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	0.9893	15	1.8422	0.5370	0.474960
Time (T)	2	0.1201	30	0.0653	1.8392	0.176414
T x G	2	0.0034	30	0.0653	0.0522	0.949232

Carotid

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	2	0.683	17	2.405	0.284	0.756369
Time (T)	2	0.081	34	0.359	0.225	0.799517
T x G	4	0.193	34	0.0359	0.539	0.708359

Exercising Carotid vs. Control

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	0.162	18	2.338	0.0694	0.795254
Time (T)	2	0.153	36	0.358	0.4276	0.655336
T x G	2	0.038	36	0.358	0.1073	0.858519

Cross-Sectional Arterial Compliance

One-hand vs. Two-hand vs. Control

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	2	0.000290	28	0.000292	0.9930	0.383145
Time (T)	2	0.000142	56	0.000068	2.0994	0.132065
T x G	4	0.000045	56	0.000068	0.6679	0.616987

Exercising arm vs control

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	0.000024	29	0.000302	0.0789	0.780791
Time (T)	2	0.000182	58	0.000066	2.7704	0.070941
T x G	2	0.000081	58	0.000066	1.2395	0.297082

Non-exercising arm vs. control

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	0.000135	15	0.000247	0.5467	0.471094
Time (T)	2	0.000056	30	0.000066	0.8419	0.440820
T x G	2	0.000167	30	0.000066	2.5324	0.096330

Carotid

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	2	0.012188	17	0.003568	3.4139	0.056702
Time (T)	2	0.001772	34	0.000771	2.2992	0.115740
T x G	4	0.000659	34	0.000771	0.8648	0.500790

Exercising Carotid vs. Control

Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
Group (G)	1	0.002943	18	0.004560	0.6454	0.432239
Time (T)	2	0.000786	36	0.000787	0.9985	0.378390
T x G	2	0.000253	36	0.000787	0.3214	0.727204

APPENDIX B
Raw Data

Subject Characteristics

	Age	Sex	Height (inches)	Weight (lbs)	Meds*	CAD status	Total Chol (mmol/L)	LDL (mmol/L)	HDL (mmol/L)	TG (mmol/L)	Random Gluc
1-lccs	63	M	68	209	ACE, BB, CCB	YES	4.66	1.93	0.98	2.8	6.5
1-rohcsg2	77	M	69	175	ACE, BB, Diuretic	YES	4.32	1.35	1.66	2.04	6.1
1-lncs	63	M	72	210	ACE, Diuretic	NO	4.12	2.29	1.03	2.04	6.7
1-jpcsg2	67	F	60	187	CCB	NO	3.15	0.7	1.75	1.08	5
1-jncs	74	M	68	195	CCB, ACE	NO	4.71	1.25	1.17	2.97	5
1-dlcsg3	68	M	64	160	CCB, ACE	NO	3.71	0.66	1.3	2.11	5.1
1-mscsg3	69	F	63	160	ACE, BB, Diuretic	YES	5.3	2.45	1.25	2.93	5.7
1-cbcsg3	61	M	71	200	ACE	NO	N/A	N/A	N/A	N/A	N/A
1-plcsg3	57	M	68	150	ACE	NO	6.07	1.22	1.51	4	5.5
1-bhcs	64	M	71	180	ACE	NO	4.91	3.14	0.84	2.63	5.8
2-hhcs	75	F	63.5	183	ACE	NO	6.86	4.16	1.32	3.63	6
2-abcs	67	M	68.5	166	Diuretic	YES	3.84	1.29	0.95	2.3	5.2
2-pbcsg3	67	F	N/A	N/A	ACE, BB, CCB	NO	3.62	0.9	1.19	2.02	5.9
2-jgcsg3	56	M	71	195	N/A	NO	N/A	N/A	N/A	N/A	N/A
2-jdcsg3	63	M	76	176	ACE, BB	YES	4.73	2.7	1.01	2.48	4.9
2-dkcsg3	39	M	76 in	260	N/A	NO	6.28	2.85	1.17	3.8	5.7
2-hocsg3	68	F	66.5	165	CCB, Diuretic	NO	N/A	N/A	N/A	N/A	N/A
c-bdcsg2	66	F	65	149	Diuretic	NO	5.24	0.94	1.85	2.96	4.9
c-nccsg2	68	F	65	211	ACE	YES	N/A	N/A	N/A	N/A	N/A
c-smcs	66	F	62.5	113	Atacand	YES	N/A	N/A	N/A	N/A	N/A
c-wmcsg3	64	M	70	194	ACE	NO	5.45	2.24	1.08	3.34	5.9
c-ejcsg3	70	F	61.5	164	BB	YES	N/A	N/A	N/A	N/A	N/A

*Meds: BB=beta blocker, CCB=calcium channel blocker; ACE=angiotensin-converting enzyme inhibitor

Systolic Blood Pressure (mmHg)

One-Hand Group

Subject	Pre	4-Week	8-Week
1-bhcs	150.7	154.0	126.7
1-jncs	134.3	140.0	134.0
1-lccs	126.0	133.0	132.0
1-lncs	156.7	140.0	149.3
1-rohcsg2	137.7	142.3	144.3
1-jpcsg2	153.3	143.7	146.7
1-plcsg3	135.7	123.7	130.3
1-cbcsg3	145.3	137.3	133.7
1-mscsg3	141.7	127.0	114.7
1-dlcsg3	119.3	112.0	111.7
MEAN	140.1	135.3	132.3
SEM	4.06	4	4.1

Two-Hand Group

Subject	Pre	4-Week	8-Week
2-hhcs	158.7	141.7	144.7
2-abcs	150.0	117.3	122.0
2-dkcsg3	128.0	129.3	130.0
2-jgcsg3	134.7	126.7	115.3
2-jdcsg3	111.7	105.3	109.3
2-hocsg3	125.3	114.7	122.3
2-pbcsg3	141.7	136.7	129.3
MEAN	135.7	124.5	124.7
SEM	4.9	4.7	4.9

Control Group

Subject	Pre	4-Week	8-Week
c-bdcsg2	146.0	145.7	136.3
c-wmcsg3	121.3	116.0	111.3
c-ejcsg3	143.0	126.7	120.7
c-nccsg2	137.3	144.3	153.7
c-smcs	135.0	119.3	137.3
MEAN	134.4	128.5	133.2
SEM	5.2	5.1	5.3

Diastolic Blood Pressure (mmHg)

One-Hand Group

Subject	Pre	4-Week	8-Week
1-bhcs	97.3	85.0	84.0
1-jncs	69.7	88.7	81.7
1-lccs	69.3	75.7	79.7
1-lncs	85.0	82.0	79.3
1-rohcsg2	65.3	66.3	65.7
1-jpcsg2	83.3	87.7	81.7
1-plcsg3	83.3	70.3	76.7
1-cbcsg3	92.0	85.3	83.7
1-mscsg3	65.7	62.7	55.7
1-dlcsg3	74.7	71.7	73.0
MEAN	75.6	77.5	76.1
SEM	2.9	2.8	2.6

Two-Hand Group

Subject	Pre	4-Week	8-Week
2-hhcs	64.7	76.0	72.7
2-abcs	79.0	60.0	61.0
2-dkcsg3	80.7	81.3	79.3
2-jgcsg3	82.7	75.3	70.7
2-jdcsg3	66.0	63.0	71.7
2-hocsg3	61.3	55.7	56.0
2-pbcsg3	76.7	77.3	75.0
MEAN	73.0	69.8	69.5
SEM	3.5	3.3	3.1

Control Group

Subject	Pre	4-Week	8-Week
c-bdcsg2	69.0	67.0	59.7
c-wmcsg3	72.3	68.7	69.7
c-ejcsg3	69.0	61.3	59.3
c-nccsg2	67.0	68.7	73.3
c-smcs	67.0	57.0	66.0
MEAN	67.2	65.5	66.8
SEM	3.8	3.6	3.3

Mean Arterial Pressure (mmHg)

One-Hand Group

Subject	Pre	4-Week	8-Week
1-bhcs	115.1	108.0	98.2
1-jncs	91.2	105.8	99.1
1-lccs	88.2	94.8	97.1
1-lncs	108.9	101.3	102.7
1-rohcsg2	89.4	91.7	91.9
1-jpcsg2	106.7	106.3	103.3
1-plcsg3	100.8	88.1	94.6
1-cbcsg3	109.8	102.7	100.3
1-mscsg3	91.0	84.1	75.3
1-dlcsg3	89.6	85.1	85.9
MEAN	99.1	96.8	94.8
SEM	2.8	2.8	2.5

Two-Hand Group

Subject	**Pre**	**4-Week**	**8-Week**
2-hhcs	96.0	97.9	96.7
2-abcs	102.7	79.1	81.3
2-dkcsg3	96.4	97.3	96.2
2-jgcsg3	100.0	92.4	85.6
2-jdcsg3	81.2	77.1	84.2
2-hocsg3	82.7	75.3	78.1
2-pbcsg3	98.3	97.1	93.1
MEAN	93.9	88.0	87.9
SEM	3.3	3.4	3

Control Group

Subject	**Pre**	**4-Week**	**8-Week**
c-bdcsg2	94.7	93.2	85.2
c-wmcsg3	88.7	84.4	83.6
c-ejcsg3	93.7	83.1	79.8
c-nccsg2	90.4	93.9	100.1
c-smcs	89.7	77.8	89.8
MEAN	89.6	86.5	89.0
SEM	3.6	3.6	3.3

Pulse Pressure (mmHg)

One-Hand Group

Subject	Pre	4-Week	8-Week
1-bhcs	53.3	69.0	42.7
1-jncs	64.7	51.3	52.3
1-lccs	56.7	57.3	52.3
1-lncs	71.7	58.0	70.0
1-rohcsg2	72.3	76.0	78.7
1-jpcsg2	70.0	56.0	65.0
1-plcsg3	52.3	53.3	53.7
1-cbcsg3	53.3	52.0	50.0
1-mscsg3	76.0	64.3	59.0
1-dlcsg3	44.7	40.3	38.7
MEAN	61.5	57.8	56.2
SEM	4	3.3	4

Two-Hand Group

Subject	Pre	4-Week	8-Week
2-hhcs	94.0	65.7	72.0
2-abcs	71.0	57.3	61.0
2-dkcsg3	47.3	48.0	50.7
2-jgcsg3	52.0	51.3	44.7
2-jdcsg3	45.7	42.3	37.7
2-hocsg3	64.0	59.0	66.3
2-pbcsg3	65.0	59.3	54.3
MEAN	62.7	54.7	55.2
SEM	4.8	3.9	4.8

Control Group

Subject	Pre	4-Week	8-Week
c-bdcsg2	77.0	78.7	76.7
c-wmcsg3	49.0	47.3	41.7
c-ejcsg3	74.0	65.3	61.3
c-nccsg2	70.3	75.7	80.3
c-smcs	68.0	62.3	71.3
MEAN	67.2	63.0	66.4
SEM	5.2	4.2	5.2

Carotid Compliance

One-Hand Group

Subject	Pre	4-Week	8-Week
1-bhcs	0.098689	0.092898	0.061636
1-jncs	0.123486	0.092688	0.119755
1-lccs	0.036699	0.070246	0.051723
1-lncs	0.096330	0.140161	0.118667
1-rohcsg2	0.109553	0.097449	0.071512
1-jpcsg2	0.119373	0.08023	0.142827
1-plcsg3	N/A	0.182636	N/A
1-cbcsg3	0.119194	0.081393	0.07548
1-mscsg3	0.124316	0.139153	0.127125
1-dlcsg3	0.121455	0.139131	0.248567
MEAN	0.105455	0.111599	0.113033
SEM	0.009274	0.011496	0.020093

Two-Hand Group

Subject	Pre	4-Week	8-Week
2-hhcs	0.112868	0.129624	0.158327
2-abcs	0.066562	0.076192	0.086646
2-dkcsg3	0.176044	0.205375	0.203867
2-jgcsg3	0.138054	0.128916	0.147541
2-jdcsg3	0.188789	N/A	0.267923
2-hocsg3	0.151597	0.137011	0.227126
2-pbcsg3	0.192729	0.091613	0.136033
MEAN	0.141688	0.146349	0.188814
SEM	0.015617	0.020051	0.02327

Control Group

Subject	Pre	4-Week	8-Week
c-bdcsg2	0.082657	0.123819	0.110246
c-wmcsg3	0.082121	0.096160	0.095147
c-ejcsg3	0.120495	0.108597	0.180690
c-nccsg2	0.143213	0.120858	0.076486
c-smcs	0.108644	0.085128	0.101298
MEAN	0.107426	0.106912	0.112774
SEM	0.011634	0.007326	0.017858

Left Artery Compliance

One-Hand Group

Subject	Pre	4-Week	8-Week
1-bhcs	0.009390	0.009256	0.011373
1-jncs	0.016395	0.022367	0.015315
1-lccs	0.017319	0.02328	0.02289
1-lncs	0.019807	0.019629	0.023944
1-rohcsg2	0.017915	0.016858	0.006978
1-jpcsg2	0.024921	0.013505	0.032431
1-plcsg3	N/A	0.037234	0.027129
1-cbcsg3	0.021039	0.021023	0.022318
1-mscsg3	0.040621	0.032139	0.066462
1-dlcsg3	0.021818	0.014258	0.010055
MEAN	0.021025	0.020955	0.023889
SEM	0.002842	0.002694	0.005382

Two-Hand Group

Subject	Pre	4-Week	8-Week
2-hhcs	0.032720	0.045401	0.04463
2-abcs	0.018560	0.034469	0.016048
2-dkcsg3	0.006959	0.014894	0.010115
2-jgcsg3	0.018030	0.014754	0.018467
2-jdcsg3	0.050983	0.017746	0.039693
2-hocsg3	0.036274	N/A	0.016754
2-pbcsg3	0.024084	0.019875	0.031354
MEAN	0.026801	0.024523	0.025294
SEM	0.005467	0.005133	0.005008

Control Group

Subject	Pre	4-Week	8-Week
c-bdcsg2	0.018049	0.023221	0.045480
c-wmcsg3	0.010016	0.022568	0.024820
c-ejcsg3	0.014697	0.020680	0.039924
c-nccsg2	0.020513	0.040739	0.017575
c-smcs	0.032552	0.033468	0.030082
MEAN	0.019165	0.028135	0.031576
SEM	0.003781	0.003860	0.005034

Right Artery Compliance

One-Hand Group

Subject	Pre	4-Week	8-Week
1-bhcs	0.039199	N/A	0.027231
1-jncs	0.030580	0.031406	0.032578
1-lccs	0.047934	0.046447	0.044670
1-lncs	0.033314	0.011925	N/A
1-rohcsg2	0.014600	0.008599	0.013931
1-jpcsg2	0.049430	0.008972	0.030802
1-plcsg3	N/A	0.032562	0.031275
1-cbcsg3	0.022823	0.018801	0.018386
1-mscsg3	0.016666	0.019767	0.027384
1-dlcsg3	0.027336	0.027336	0.018500
MEAN	0.031320	0.022868	0.027195
SEM	0.004172	0.004225	0.003103

Two-Hand Group

Subject	Pre	4-Week	8-Week
2-hhcs	0.027262	0.037213	0.039634
2-abcs	0.019002	0.035575	0.017347
2-dkcsg3	0.019828	0.016742	0.028557
2-jgcsg3	0.035750	0.028097	0.025153
2-jdcsg3	0.049263	0.034119	0.057875
2-hocsg3	0.016956	N/A	0.050190
2-pbcsg3	0.012449	0.018046	0.014175
MEAN	0.025787	0.028299	0.033276
SEM	0.004855	0.003674	0.006246

Control Group

Subject	Pre	4-Week	8-Week
c-bdcsg2	0.012339	0.018941	0.016130
c-wmcsg3	0.012414	0.004577	0.009594
c-ejcsg3	0.017811	0.031092	0.024694
c-nccsg2	0.018877	0.018077	0.020081
c-smcs	0.032811	0.027587	0.043280
MEAN	0.018851	0.020055	0.022756
SEM	0.003740	0.004600	0.005698

APPENDIX C
Reproducibility

Reproducibility

Introduction

This study was performed to investigate the reproducibility of blood pressure measurements with applanation tonometry. The force at which the pencil-type probe is held down over the artery can affect baseline arterial blood pressure values. Therefore, the variability in using the pencil-type tonometer probe between and within investigators was evaluated to assess its possible effects on arterial blood pressure measurements taken throughout the primary investigation.

Methods

Four male participants ranging in age from 63 to 74 years, were recruited from the primary isometric handgrip training study. Two subjects had participated in the isometric leg training, one in the one-hand isometric handgrip and one from the two-hand isometric handgrip training. Participants were recruited based on letters from the investigators. After consenting to participate in the study, subjects were instructed to monitor their diet and exercise level prior to attending the first testing session and to keep it the same prior to the second testing session. Participants were tested at two different testing sessions, at approximately the same time of day, one week apart. Upon arrival in the laboratory, the participant's skin was prepared with gentle abrasion and cleaned with rubbing alcohol before the placement of 2 sets of electrodes in the modified V5 position. The electrocardiogram (ECG) signal (model Cardiomatic MSC 7123, Medical Systems Corp, USA) was utilized to coordinate the timing for the analysis of blood pressures acquired over one QRS complex. Continuous blood pressure measurements were made with an

automatic inflatable oscillometric cuff positioned on the upper arm and an automated tonometer over the radial artery (model CBM-7000, Colin Medical Instruments, San Antonio, USA). Direct blood pressure measurements over the artery of interest were obtained with a hand-held pencil like tonometer probe containing a high-fidelity strain-gauge transducer (model SPT-301, Millar Instruments Inc., Texas, USA). The analogue outputs from the radial tonometer, pencil tonometer and ECG were sampled at 200Hz through an analog-to-digital converter (model ML795, ADInstruments, Colorado Springs, USA) to allow data acquisition and subsequently stored on a personal computer (IBM Netvista x86 compatible processor, White Plains, USA) using data acquisition software (Chart 4.2, ADInstruments, Colorado Springs, USA).

Once the ECG and blood pressure readings stabilized, investigators began to record blood pressure measurements over the artery of interest. Thirty seconds of stable blood pressure waveforms were collected for each investigator over the carotid artery, the left brachial artery and the right brachial artery, sampled at 200Hz through an analog-to-digital converter (model ML795, ADInstruments, Colorado Springs, USA) to allow data acquisition and subsequently stored on a personal computer (IBM Netvista x86 compatible processor, White Plains, USA) using data acquisition software (Chart 4.2, ADInstruments, Colorado Springs, USA). Waveforms produced by the pencil type tonometer over each artery of interest were analyzed using Chart 4.2 software to determine minimum values (diastolic pressure), maximum values (systolic pressure) and mean arterial pressures.

The pressure values obtained were exported to Excel (Microsoft Office version 2000) where the tonometer signals at the artery of interest were calibrated and pulse pressure was determined as

$$\text{Pulse Pressure} = Ds - Dd \qquad \text{(equation \#1)}$$

where, Ds = maximum (systolic) diameter
Dd = minimum (diastolic) diameter

Pulse pressure values at the carotid, left and right brachial arteries were determined for each investigator at each testing session. Variability between investigators was determined according to the following formula

$$\text{Coefficient of variation} = (SD/\text{Mean}) \times 100 = SD/\frac{(PP_a + PP_b)}{2} \times 100 \qquad \text{(equation \#2)}$$

where, SD = standard deviation
PP_a = Pulse pressure investigator A
PP_b = Pulse pressure investigator B

The coefficient of variation was determined for the carotid, left and right brachial arteries for each participant at each testing session.

Variability within investigators was determined according to the following formula

$$\text{Coefficient of variation} = (SD/\text{Mean}) \times 100 = SD/\frac{(PP_1 + PP_2)}{2} \times 100 \qquad \text{(equation \#3)}$$

where, SD = standard deviation
PP_1 = Pulse pressure Time 1
PP_2 = Pulse pressure Time 2

Results

Between investigator variability

Statistical analysis revealed coefficient of variations between investigators of 0.18% to 12.74% for the carotid artery (Table 1).

Table 1: Coefficient of variation for the carotid artery

	Time 1	Time 2
AB	4.97	4.68
JN	7.51	12.74
KK	0.18	1.94
LH	3.96	7.40

Coefficients of variations of 0.82% to 7.68% were found for variability between investigators for the left brachial artery (Table 2).

Table 2: Coefficient of variation for the left brachial artery

	Time 1	Time 2
AB	1.52	1.53
JN	4.77	3.55
KK	4.70	0.82
LH	4.13	7.68

Statistical analysis revealed coefficients of variations between investigators of 1.80% to 26.13% for the right brachial artery (Table 3).

Table 3: Coefficient of variation for the right brachial artery

	Time 1	Time 2
AB	7.13	9.73
JN	5.50	6.59
KK	26.13	8.71
LH	1.80	2.86

Within investigator variability

Coefficients of variation for within investigator variability in investigator A were between 1.83% and 26.95% (Table 4).

Table 4: Coefficient of variation for investigator A

	Carotid	LBA	RBA
AB	11.35	4.08	19.89
JN	15.34	13.22	4.33
KK	1.83	3.15	10.31
LH	14.88	26.95	22.61

Statistical analysis revealed coefficients of variation for within investigator variability in investigator B of 0.29% to 26.00% (Table 5).

Table 5: Coefficient of variation for investigator B

	Carotid	LBA	RBA
AB	1.72	4.08	17.33
JN	4.89	4.93	3.24
KK	0.29	0.74	7.38
LH	26.00	15.40	18.04

Conclusions

Repeatability of a measurement is related to the ability to determine an association with an outcome (40). Variation in measurement can occur due to between and within investigator variability. Between investigators variability fell between 0.18% and 26.13%. Although the variability was high on some occasions (26.13%) the majority of values were below 10%, a generally acceptable value. Within investigator variability was comparable for both investigators A and B. Equipment sources of variability and inherent variability in the arteries themselves may also have contributed to the coefficients of

variations determined. Intraclass correlational coefficients could also be used to assess the repeatability of a measurement, however due to the small sample size, coefficients of variation were used.