ARTERIAL ADAPTATIONS TO RESISTANCE EXERCISE TRAINING

ARTERIAL COMPLIANCE, BRACHIAL ENDOTHELIAL FUNCTION AND BLOOD PRESSURE ADAPTATIONS TO RESISTANCE TRAINING IN YOUNG HEALTHY MALES

By

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ABSTRACT

The current study evaluated the potentially detrimental effects of daily resistance training on cardiovascular health using a longitudinal study design. This study also addressed the effects of resistance training on vascular endothelial function.

Recent cross-sectional studies have shown resistance trained individuals have reduced whole-body arterial compliance compared to sedentary controls and that the age-associated reduction of arterial compliance is augmented in resistance trained athletes. The effect of resistance training on vascular endothelial function has not been addressed to date in the literature.

Twenty-eight young healthy males (age: 23±3.9 [mean±SD]) were whole body resistance trained five times a week for twelve weeks, using a split body design. Measurements of supine resting arterial blood pressure at the brachial artery, carotid, brachial and femoral cross-sectional compliance, and brachial vascular endothelial function (using flow-mediated dilation) were acquired prior to, halfway through and following the exercise training protocol.

Strength of various body segments increased significantly following the resistance training program. Shoulder press one repetition maximum (1RM) lifts increased from 141.4±7.6 lbs. to 185.2±8.8 lbs. and double leg press 1RM from 483.0±29.0 lbs. to 859.8±52.1 lbs. Resting diastolic blood pressure increased significantly from Mid to Post training (61.8±1.3 mmHg to 65.4±1.2 mmHg) yet was not significantly changed from Pre values (62.9±1.2 mmHg). Pulse pressure was reduced significantly with exercise training by the Post training time-point (Pre 63.3±1.9 mmHg; Mid 59.0±2.4 mmHg; Post

53.7±2.8 mmHg). Mean arterial carotid and femoral artery diameters were not changed with resistance training; however, mean brachial artery diameter increased by the Mid training time-point and remained elevated at the Post training time-point (Pre 3.81±0.10 mm; Mid 4.03±0.10 mm; Post 4.04±0.11 mm). Cross-sectional compliance did not change at the carotid or the brachial arteries, however the femoral artery experienced a reduction of compliance by the Mid time-point that remained to the Post training time-point (Pre 0.162±0.012 mm^2/mmHg; 0.125±0.013 mm^2/mmHg; Post 0.129±0.015 mm^2/mmHg). Brachial vascular endothelial function measured using flow-mediated dilation did not show a significant change with resistance training. When normalized for shear rate (which was also unaltered with resistance training) there were no changes in endothelial function. Peak and 10-s average brachial post-occlusion blood flow was enhanced with resistance training (Pre 247.5±14.0 ml/min; Mid 331.1±18.5 ml/min; Post 290.5±21.0 ml/min) possibly revealing enhanced resistance vessel function.

In conclusion, resistance exercise training results decreased PP, reduced femoral compliance, an increase in mean brachial artery diameter and enhanced post-ischemic blood flow. The exact mechanisms responsible for such changes remain unknown and require further investigation.

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SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial blood pressure
PP	Pulse pressure
MBV	Mean blood velocity
MBF	Mean blood flow
CSC	Cross sectional compliance
FMD	Flow mediated dilation
MWSR	Mean wall shear rate
d	diameter
r	radius
ROI	region of interest
f_d	frequency difference
f_t	transmitted frequency
f_r	received frequency
v	velocity
0	angle of insonation
c	speed of sound in tissue
1RM	One repetition maximum

CHAPTER 1

REVIEW OF LITERATURE

1.1 INTRODUCTION

The arterial system is responsible for the movement of blood from the heart to various parts of the body. During an acute bout of exercise, the physical and chemical stresses placed on the arterial system are numerous and large in magnitude. Thus, exercise training (multiple sessions in succession) produces adaptations to this system, which are intensity and duration dependent. Different exercise modalities result in variations to the physical and chemical stresses placed on the arterial system. Resistance exercise training is an exercise modality characterized as a method to produce muscle hypertrophy and motor unit recruitment adaptations. However, the effects of resistance training on the arterial system have received little attention or focus in the literature.

The health of the arterial system is often evaluated using functional and structural measurements. Most common is the measurement of resting arterial blood pressure and its constituents including systolic (SBP), diastolic (DBP), mean arterial pressure (MAP) and pulse pressure (PP). Structural measurements of the arterial system measurements include arterial compliance or stiffness, changes in arterial diameter and intima-media thickness, while functional evaluations include measurements of dilation and constriction of arteries subjected to various physical and chemical stimuli.

Exercise training has been acknowledged as an effective non-pharmacological therapy used to treat some disease processes associated with the structure and function of

the arterial system (Kingwell, 2002). However, the modality of choice for exercise prescription in arterial disease has most often been aerobic or endurance based exercise programs. In addition, considerable debate exists regarding the impact of resistance exercise training on blood pressure and arterial compliance. The effects of resistance training on endothelial function, a functional assessment of the arterial system, have not been studied to date.

1.2.1 Resting blood pressure

Arterial pulse waves were first recorded and described early in the 19th century by Carl Ludwig, however; measurements of SBP and DBP became popular due to the simplicity with which it may be measured (Zimmer, 1999).

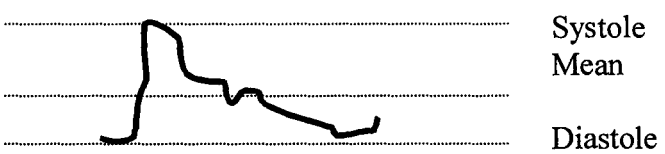

Figure 1.1 Tracing of a blood pressure wave with labels of systole, mean, and diastole.

The arterial pressure wave was subsequently divided into four different constituents that described its shape. SBP describes the peak pressure while DBP describes the lowest pressure during the cardiac cycle. Whereas, MAP describes the average blood pressure exerted on the arterial wall and PP is simply the difference between the SBP and DBP points. Subsequently, elevated resting SBP and DBP was one of the first cardiovascular measurements identified as an independent risk factor in the establishment and

progression of cardiovascular disease (Greenland, LaBree, Azen, Doherty, & Detrano, 2004). Elevated PP as surrogate measure of reduced compliance or reduced arterial compliance itself have more recently been identified as possible mechanisms responsible for arterial remodeling (Laurent et al., 2001) and the progression of coronary artery disease, respectively (Arnett, Evans, & Riley, 1994; Hodes, Lakatta, & McNeil, 1995; Rowe, 1987).

1.2.2 Acute cardiovascular responses to resistance exercise

During resistance exercise there is a large pressor reflex, which places extreme stress on the arterial system. Heart rate increases rapidly along with a subsequent increase in blood pressure due to central drive. This stress has been measured using intra-arterial pressure transducers in healthy (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985) and elderly (McCartney, McKelvie, Martin, Sale, & MacDougall, 1993) men while they performed double-leg press or indirectly using post-exercise measurements of brachial arterial blood pressure (Wiecek, McCartney, & McKelvie, 1990). MacDougall and colleagues (1985) measured intra-arterial pressure values in excess of 360/280 mmHg, which far surpassed measurements at the brachial artery following acute exercise (MacDougall et al., 1992; MacDougall et al., 1985). These high values of arterial blood pressure persist with training if the protocol is progressive and testing is performed at the same relative intensity both prior to and following training (McCartney et al., 1993). However, at the same absolute intensity blood pressure is reduced compared to pre-training values in populations of young healthy males (Sale, Moroz, McKelvie, MacDougall, & McCartney, 1994) and in older adults (McCartney et

al., 1993). Further studies have identified the point of peak arterial blood pressure as the point of greatest effort by the participant during a specific movement (MacDougall et al., 1992). The contraction pattern (weight-lifting vs. isokinetic) of the specific exercise influences peak arterial pressure in that weight-lifting exercises result in higher peak SBP and DBP (Sale, Moroz, McKelvie, MacDougall, & McCartney, 1993). In addition, repeated repetitions to failure produce greater acute blood pressure responses compared to 1RM (Sale et al., 1993).

Measuring the rate-pressure product (heart rate multiplied by the MAP) is another method used to determine acute cardiovascular stress. Benn, McCartney and McKelvie (1996) used this measurement to estimate cardiac work while elderly participants performed various tasks including stair-climbing, treadmill walking and resistance exercise (single arm curls and double leg press). Although work rates were not equal amongst the various exercises, similar rate-pressure products were observed suggesting sufficient perfusion of cardiac tissue when performing high-intensity resistance training (Benn, McCartney, & McKelvie, 1996). Although the rate-pressure product gives a good indication of cardiac work, it does not isolate the acute tensile stresses of exercise on the arterial vascular system.

One final component that affects the acute response of blood pressure during resistance training is the Valsalva maneuver. Described as a forced expiration against a closed epiglottis, the Valsalva maneuver is believed to be effective in stabilizing the trunk and abdomen during heavy lifting (Narloch & Brandstater, 1995). In one study, when the use of the Valsalva maneuver was eliminated by expiring during lifting, a reduction in

both arterial blood pressure and potentially the stress experienced by the central arterial vessels (the aorta) were achieved (Narloch & Brandstater, 1995). However, recent research suggests a brief valsalva may play a protective effect on cardiovascular system. This protective effect has been observed in both cerebral vessels (M. J. Haykowsky, Eves, DE, & Findlay, 2003) and the left ventricle (M. Haykowsky, Taylor, Teo, Quinney, & Humen, 2001).

1.2.3 Resting blood pressure and resistance exercise training

Resistance training has been recently advocated as a viable exercise modality for long-term reductions of arterial blood pressure (Fleck, 1988; Hagberg et al., 1984; G. Kelley, 1997; G. A. Kelley & Kelley, 2000; Martel et al., 1999; Wiley, Dunn, Cox, Hueppchen, & Scott, 1992). Apparent reductions have been observed in numerous populations including the elderly (Martel et al., 1999), hypertensive adolescents (Hagberg et al., 1984), and young sedentary subjects (Carter, Ray, Downs, & Cooke, 2003). However, some research argues against its effectiveness in reducing resting arterial blood pressure (Blumenthal, Siegel, & Appelbaum, 1991; Cononie et al., 1991; Van Hoof et al., 1996). When comparing literature, variations in study population, study design, resistance exercise protocol and blood pressure measurement methods make definitive conclusions difficult.

Comparison studies involving precisely selected controls based on age, gender, and body composition support the argument that resistance training reduces resting blood pressure. An early study showed weight lifters have lower resting heart rates and a lower resting SBP than sedentary controls (Smith & Raven, 1986). Although this comparison

may be of interest it is not ideal since it is a comparison between trained and sedentary subjects.

Recently, longitudinal studies supporting a beneficial effect of resistance training on resting blood pressure have been conducted allowing possible cause and effect relationships to be explored (Carter et al., 2003; Hagberg et al., 1984; Harris & Holly, 1987). Hagberg and colleagues (1984) conducted one of the first longitudinal studies involving weight training that focused on the response of resting blood pressure. The researchers had a group of sedentary hypertensive adolescents complete an endurance training protocol followed by a resistance exercise program. Significant reductions in SBP and DBP from 143/88 mmHg to 130/77 mmHg were observed in response to 5 months of endurance training. This initial reduction following endurance training was followed by a further reduction in resting blood pressure to 126/73 mmHg over the course of the subsequent five months of resistance training. Although this further decline was not statistically significant, this maintenance effect of weight training on blood pressure persisted even though gains in VO_{2max} accomplished through endurance training were abolished by the end of the weight training period. Although positive, this study had major limitations restricting extrapolation of these findings. First, there was a limited sample size involving a specific population of hypertensive adolescents. Second, the effects of resistance training were confounded by the cessation of endurance training (ie. detraining effects). Harris and Holly (1987) explored circuit weight training in young (average age of 32.1 years) borderline hypertensive subjects without prior endurance training. Their results indicated no change in SBP yet DBP did show significant

reductions (Harris & Holly, 1987). However, the exercise stimulus consisted of high repetitions, low resistance, and little rest between exercises or sets, essentially creating an aerobic stimulus. Recently, Carter and colleagues (2003) have shown significant reductions of both SBP and DBP of 9 mmHg and 8 mmHg, respectively in young normotensive subjects following 8 weeks of whole body resistance training at a frequency of 3 sessions per week. Their resistance training protocol was progressive with participants completing 3 x 10 reps of ten exercises while reevaluating 1RM periodically to maintain the training stimulus Thus, significant reductions in resting arterial blood pressure are evident in the literature, however study limitations are extensive.

Equivocal effects of resistance training on ambulatory or resting blood pressure permeate the literature (Blumenthal et al., 1991; Cononie et al., 1991; Van Hoof et al., 1996). Cononie and colleagues (1991) evaluated the effect of different types of exercise training on resting blood pressure in an elderly population. Subjects were either endurance trained or resistance trained for a period of six months, with participants in the resistance trained showing no reductions of resting SBP or DBP (Cononie et al., 1991). The experimental design may have influenced these results since, resistance training sessions were of a rather low intensity and work performed was not matched to that of the endurance group. In a study by Blumenthal and colleagues (1991) in which participants were either trained aerobically or resistance trained, reductions of blood pressure did not occur. Interestingly, the aerobically trained group did not see reductions of either SBP or DBP, which has been noted throughout the literature. In addition, the researchers merely used the resistance-trained group as a control for the psychosocial effects of exercise

training. Thus, the actual performance of resistance exercise and improvements in performance were not the primary objective of the study. Van Hoof and colleagues (1996) further supported the lack of a blood pressure reduction following sixteen weeks of resistance training in young healthy males. No changes in a variety of blood pressure measurements including resting seated, supine, 24 hour ambulatory, and during submaximal cycling activity, were evident when compared to a well-matched sedentary control group (Van Hoof et al., 1996). Similar intervention study results indicate no blood pressure changes in females (Katz & Wilson, 1992) following high-intensity resistance training (Hurley et al., 1984), or in those exhibiting several coronary risk factors (Hurley et al., 1988).

Few studies have shown a negative impact of resistance exercise on resting arterial blood pressure; however, cross-sectional data may give this impression. Numerous studies have compared resting SBP and DBP in weightlifters or power athletes and aerobically trained counterparts (Lehmann & Keul, 1984). Lehmann & Keul (1984) indicated a significantly higher incidence of hypertension in weight-trained individuals compared to cyclists and long-distance runners. Similar comparison studies have shown higher blood pressure values in weight-trained individuals compared to aerobically trained athletes (Kumagai, Nishizumi, & Kondo, 1988; Longhurst, Kelly, Gonyea, & Mitchell, 1980). Although not positive, these studies compare a population with a reduced risk of hypertension (endurance trained athletes) to a group of athletes who may have nutritional (high protein consumption) and hormonal (testosterone) differences.

In summary, the majority of studies looking at the effects of weight training on blood pressure indicate little, if any beneficial effect. However, comparisons between the different studies are difficult since training protocols, methods, blood pressure measurements and populations differ. The following section describing two meta-analysis on the topic of resistance training and resting blood pressure further support the need for more studies before definitive conclusions can be made.

1.2.4 Meta-analysis of resistance training and resting blood pressure

Meta-analysis is a method of quantitative research in which individual studies addressing a common problem are statistically combined to arrive at conclusions about a body of research (Baumgartner, Strong, & Hensley, 2002). For this reason, conclusions that arise from meta-analysis are invaluable and relatively unbiased. Kelley (1997) was the first to analyze the available research regarding the effect of dynamic resistance exercise on resting blood pressure. This meta-analysis covered all relevant studies from January 1966- to December 1995. Inclusion criteria included the following: 1) subjects were adults aged 18 or older, 2) dynamic resistance exercise was the only method of training, 3) training duration was not a limitation, 4) changes in resting SBP and DBP needed to be reported, 5) non-exercise control group needed to be included, and 6) studies needed to be published in journals. After elimination of studies that did not meet the inclusion requirements, nine relevant studies remained. Within these nine studies, 144 exercise participants were compared to 115 control subjects. Results indicate a reduction of SBP and DBP of between 3 to 4%. This magnitude of blood pressure reduction may not seem of clinical importance; however, it has been show that a 5 mmHg

reduction in resting blood pressure decreases stroke incidence by 40% and myocardial infarction by ~15% (G. Kelley, 1997). While these results do sound promising, the author suggests some limitations concerning this analysis. First and most significant is the lack of relevant research in this area. In particular, the author was only able to find nine studies with a small total number of subjects with which to perform the analysis. Second, many of the studies that were included did not have adequate data to make ideal comparisons between studies.

More recently, Kelley and Kelley (2000) endeavor to address some of the inadequacies of the first meta-analysis. This second meta-analysis differs slightly from the first one, in that it included some unpublished data, however many of the same studies are included. As well, this second meta-analysis includes recent papers published between January 1996 and December 1998 that were not initially included. A total of 320 participants (182 exercisers, and 138 controls) were included. With all these similarities it is not surprising that the results of the second meta-analysis are very similar Nevertheless, reductions in SBP ranged between 2 to 4%. Once again, the authors suggested further research is needed to precisely determine the effectiveness of resistance training as a non-pharmalogical alternative in blood pressure reduction. The authors also express a need for more studies involving hypertensive subjects, since there is a lack of research regarding this population that could potentially benefit most from this treatment.

1.3 Arterial compliance

Arterial compliance is a measurement of an artery's ability to accommodate further increases in volume (Dart & Kingwell, 2001). PP, which is calculated as the

difference between SBP and DBP, has been established as representative of arterial stiffness and when elevated, is considered an independent risk factor for cardiovascular mortality in many populations (Benetos, Rudnichi, Safar, & Guize, 1998; Benetos et al., 1997). Although PP is a simple and quick measurement to obtain, it does not directly measure arterial stiffness (Arnold, 1990). Thus, arterial compliance measured non-invasively using pulse wave velocity (PWV) or ultrasound evaluation is becoming more prominent both in research and clinical settings. These more direct methods enable a fairly comprehensive evaluation of the health of the arterial system. In addition, through the application of ultrasound methods, determinations of arterial compliance may be made in both central and peripheral arteries.

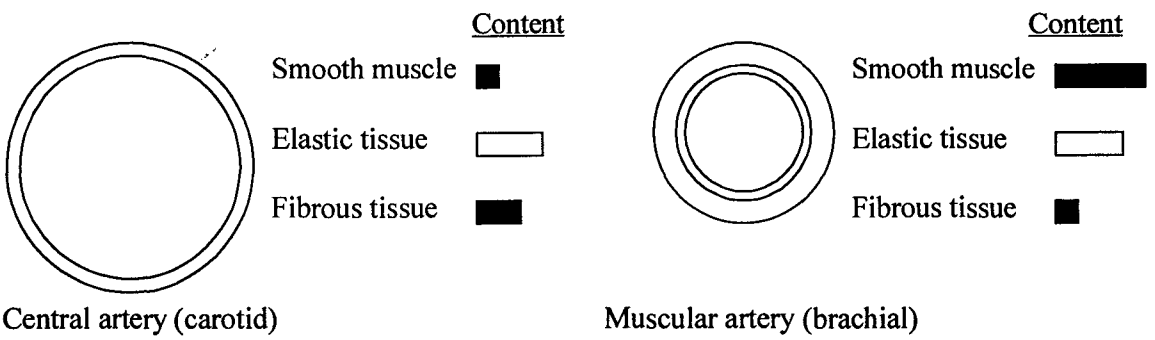

Figure 1.2 Central and muscular artery differences in structure and content (Adapted from Berne and Levy, 2001).

The central arterial system, consisting of the aorta and its major braches, is responsible for accommodating the relatively large volume of blood during systole (Dart & Kingwell, 2001) and ensuring continuous blood flow throughout the remainder of the cardiac cycle, especially in the coronary circulation (McVeigh et al., 1999). With aging there is a

concomitant reduction of arterial compliance, which is accompanied by intimal-media thickening, structural alterations in the vascular media including reduced elastin and increased collagen content (Lakatta, 2003). In addition, the regulation of vascular smooth muscle tone may alter arterial compliance on a chronic basis (Lakatta & Levy, 2003). Reduced arterial compliance has also been found to predict various disease processes including coronary events in hypertensive patients (Boutouyrie et al., 2002), insulin-dependent diabetes mellitus (Berry, Skyrme-Jones, Cameron, O'Brien, & Meredith, 1999), and coronary artery disease (Gatzka, Cameron, Kingwell, & Dart, 1998; Hirai, Sasayama, Kawasaki, & Yagi, 1989).

1.3.1 Measuring arterial compliance

Measuring arterial compliance in humans must be accomplished using indirect techniques, since obtaining vascular tissue and directly testing stress-strain relationships is not feasible. Two methods have been developed and will be outlined in this review. The pulse wave velocity technique (PWV) evaluates the general stiffness of an artery through measurement of the speed of a pulse wave propagating along a portion of a vessel. The assessment of arterial compliance of specific areas of the circulatory system (carotid or brachial arteries) requires those arteries to be visualized with Ultrasound or magnetic resonance imaging in conjunction with simultaneous blood pressure measurements (O'Rourke, Staessen, Vlachopoulos, Duprez, & Plante, 2002).

Of these two techniques PWV requires the least expertise, thus increasing its appeal and popularity. Measurements of PWV consist of recording blood pressure or flow simultaneously at two different sites of the circulatory system. For example, blood

flow measured at the aortic root using ultrasound Doppler is simultaneously recorded along with blood pressure obtained with arterial tonometry or oscillometry at a distal artery. The time difference between the initial point of aortic outflow and the blood pressure upstroke is compared to the distance the pulse wave has traveled (Vaitkevicius et al., 1993). A similar measure in the peripheral circulation may also be obtained by measuring the time delay between blood pressure waves recorded at the brachial and radial arteries (Nichols, Hartley, McDonald, & O'Rourke, 1998). The specificity and accuracy of the PWV technique limits its application. According to O'Rourke and colleagues (2002) measurement error arises when body surface landmarks used to measure the distance of PW travel are inaccurate. For instance, PWV measured in markedly obese participants may be overestimated because the true distance the pulse wave travels will be overestimated from surface measurements. Second, the exact length of the conduit artery of interest may be quite different from person to person due to anatomical differences. In addition, PWV technique requires an arterial system that conforms to a Winkessel model, which assumes arterial wall homogeneity and thus similar elastic qualities throughout the arterial system (O'Rourke et al., 2002).

Ultrasound imaging combined with arterial tonometry is used to evaluate arterial compliance in a specific region or specific artery such as the carotid or brachial arteries. Ultrasound imaging enables relatively accurate measurements of conduit artery diameters to be obtained throughout the cardiac cycle, which permits diameter changes to be measured. The recent development of arterial tonometry to obtain continuous arterial blood pressure has allowed arterial compliance to be measured without invasive intra-

arterial pressure transducers. An accurate continuous blood pressure measurement device has been developed which combines an arterial tonometer at the radial artery with an oscillometric measurement of brachial arterial blood pressure (Colin Medical etc.). Using the same principle, a pen-like hand-held (Millar Instruments Inc.) arterial tonometers has been developed, permitting measurements of pressure waveforms that are not different from intra-arterial measurements in various superficial arteries, such as the carotid artery (Kelly, Hayward, Avolio, & O'Rourke, 1989). By combining these three devices (ultrasound imaging, Colin and Millar) arterial compliance at central (carotid) and peripheral (brachial, femoral) arteries may be accurately determined.

1.3.2 Arterial compliance and exercise training

High levels of aerobic activity have been associated with elevated levels of arterial compliance (Gates, Tanaka, Graves, & Seals, 2003; Kakiyama, Matsuda, & Koseki, 1998; Schmidt-Trucksass et al., 1999; Vaitkevicius et al., 1993). As part of the Baltimore Longitudinal Study of Aging, Vaitkevicius and colleagues (1993) examined augmentation index (an indirect measurement of stiffness) and aortic pulse wave velocity in a population ranging from 21-96 years of age. They found an association between high aerobic fitness levels (VO_{2max}) and attenuated age-related declines of arterial stiffening. A subsequent comparison of this population revealed that older endurance trained males had lower augmentation indices and aortic pulse wave velocities than their older sedentary counterparts (Vaitkevicius et al., 1993). Kakiyama and colleagues (1998) compared healthy male subjects of various fitness levels and found a similar positive relationship between habitual physical exercise and elevated levels of aortic

distensibility. Furthermore, this relationship was dependent on the frequency and duration of physical activity, indicating an additive benefit to those with higher habitual physical activity levels (Kakiyama et al., 1998). Finally, Gates and colleagues (2003) duplicated the findings of Kakiyama et al. (1998), showing reduced aortic pulse wave velocities when comparing endurance trained to sedentary individuals of different ages. However, this observation did not influence normal age-associated increases of the left ventricle (Gates et al., 2003).

Numerous longitudinal studies have furthered cross-sectional support for increased arterial compliance with endurance training in various populations (Cameron & Dart, 1994; Ferrier et al., 2001; Moreau, Donato, Seals, DeSouza, & Tanaka, 2003; Tanaka et al., 2000). Endurance exercise has been shown to acutely increase systemic arterial compliance in healthy participants following moderate (Kingwell, Berry, Cameron, Jennings, & Dart, 1997) and maximum symptom-limited exercise (Naka et al., 2003). Studies in healthy men have shown moderate exercise (~ 60-75% of max heart rate), of limited duration (30-45 minutes), at a relatively low frequency (4-6 days/week) increases arterial compliance of central arteries after only twelve weeks independent of changes in body mass, arterial blood pressure, heart rate or other blood markers of cardiovascular risk (Tanaka et al., 2000). Similar exercise induced increases of arterial compliance have been noted in older women. These gains in arterial compliance are above those attributable to hormone replacement therapy (Moreau et al., 2003). Furthermore, these beneficial effects have been noted after relatively short periods of training lasting 4 weeks in healthy young males (Cameron & Dart, 1994). However,

these findings have not been observed in a population at risk for further cardiac events or in those with isolated systolic hypertension (Ferrier et al., 2001). A limited duration training stimulus may have contributed to these equivocal findings.

1.3.3 Mechanisms of altered arterial compliance with training

Investigators have speculated that both functional and structural adaptations contribute to training induced elevations of arterial compliance. The most likely mechanism for functional adaptation is related to alterations in vascular smooth muscle tone while possible sites of structural adaptations include: collagen, elastin, calcium content and glycosylation end-products. Mechanistic human studies related to compliance and exercise are lacking; however, several studies conducted in rats give some insight into structural adaptations of arteries with exercise training. Matsuda and colleagues (1993) were the first to directly measure the structure and content of rat aortas following regular aerobic exercise training. Although no differences in aortic diameter were evident with endurance training, elastin content was significantly elevated and calcium content in elastin was significantly reduced compared to sedentary controls possibly explaining the increased aortic compliance (Matsuda, Nosaka, Sato, & Ohshima, 1993). The investigators believed the reduced content of calcium of elastin and the total increase in elastin content would positively contribute to total elasticity, thus increasing arterial compliance. Although significant, the results of Matsuda and colleagues (1993) are limited due to the forced running procedures. A similar study was conducted in which rats had access to wheel running at their own leisure (Kingwell, Arnold, Jennings, & Dart, 1997). Similar increases in arterial compliance were apparent, independent of

functional changes of the vessel (ie. aortic reactivity); however, vessel content changes were not evaluated (Kingwell, Arnold et al., 1997).

1.3.4 Strength training and arterial compliance

Strength training induces cardiovascular stresses that may be different than those experienced with aerobic exercise particularly related to a large pressor response (MacDougall et al., 1985). Consequently, adaptations of the cardiovascular system may be divergent with strength training as compared to endurance exercise training. Bertovic and colleagues (1999) completed a cross-sectional comparison between sedentary controls and strength-trained individuals. Measurements of total systemic compliance, pulse wave velocity and proximal aortic stiffness revealed some differences between groups. Total systemic arterial compliance was significantly reduced whereas pulse wave velocity from the carotid to femoral arteries and the femoral to dorsalis pedis was not different between groups. The authors suggest these findings indicate that stiffness is localized to the proximal aorta since peripheral measures showed no stiffening. Other important findings include elevated PP at the carotid and brachial arteries suggesting stiffer arteries; however, this may also invalidate the comparison between the two groups. Particularly, the comparison of arterial compliance may have been measured on different parts of the volume-pressure curve in each group making comparisons invalid. Miyachi and colleagues (2003) attempted to reproduce previous findings by conducting a cross-sectional comparison between sedentary and resistance-trained individuals of two different age categories and using the pressure-sonograph technique. Although a trend for reduced carotid (central) compliance was apparent in young resistance-trained

participants it did not reach statistical significance (P=0.09). However, this difference was significant in middle-aged resistance-trained participants (Miyachi et al., 2003). In addition, age associated thickening of the intima-media layer was potentiated in the middle-aged resistance-trained participants indicating a possible mechanism (Miyachi et al., 2003). Although these findings are persuasive, apparent stiffening of central arteries with resistance training has not been confirmed using a longitudinal design.

1.4 Vascular endothelial function

The endothelium of conduit arteries has been identified as the primary target for injury from mechanical forces and processes related to cardiovascular risk factors such as hypertension and aging (Moyna & Thompson, 2004). Thus, the health of the endothelium plays a pivotal role in the maintenance of vascular tone and reactivity (Moncada & Higgs, 1991). Similar to, and likely related to arterial stiffening, the endothelium may become dysfunctional, losing its ability to dilate in response to a physical or chemical stimulus.

The importance of intact vascular endothelial function is well supported in the literature. In particular, endothelial dysfunction has been observed in those with coronary artery disease (Gokce et al., 2002; Takase et al., 1998), chronic heart failure (Gokce et al., 2003; Hornig, Maier, & Drexler, 1996; Linke et al., 2001) and apparent healthy elderly individuals with no overt signs of cardiovascular disease (Takase et al., 1998). Also, brachial endothelial dysfunction has been well correlated with disease progression of the coronary arteries in patients with coronary artery disease (Gokce et al., 2003).

1.4.1 Measuring vascular reactivity and function

The vascular function of arteries is commonly divided into two components, endothelial dependent and independent, and is measured using several different techniques. Endothelial dysfunction is also assessed through its association with altered circulating levels of several biomarkers including, nitric oxide products (nitrites, nitrates), C-reactive protein (independent predictor of myocardial infarction), endothelin-1 (potent vasoconstrictor), von Willebrand factor, circulating endothelial cells (CECs), and thrombomodulin.

Endothelial-dependent function in various arteries, including the coronary circulation, can be assessed using quantitative coronary angiography (Verma, Buchanan, & Anderson, 2003), or at various peripheral arteries using venous occlusion plethysmography or Ultrasound Doppler. Dilation of an artery in response to dependent and independent stimuli is quickly becoming the most convenient and direct method with which endothelial dysfunction is assessed. Specifically, ultrasound imaging enables artery diameters measured at rest to be compared to diameters measured following stimuli, such as shear stress or pharmacological agents. The non-invasive nature of peripheral measurements definitely makes this option the most appealing. As well, peripheral endothelial function measured with Ultrasound has been well correlated with endothelial function of the coronary circulation (Playford & Watts, 1998; Schroeder et al., 1999; Takase et al., 1998).

Peripheral measurements may be acquired with invasive and non-invasive methods. Invasive methods involve brachial intra-arterial catheterization with subsequent infusion of various vasoactive substances. Dose-response relationships can then be

compared between groups or at different time-points throughout an intervention timeline. Specific vasoactive substances namely acetylcholine (ACh), sodium nitroprusside (SNP), N^G-monomethyl-L-arginine (L-NMMA), and isosorbide dinititrate, are infused to evaluate endothelial dependent and independent dilation.

Briefly, acetylcholine stimulates smooth muscle relaxation through an endothelium dependent pathway. ACh stimulates muscarinic receptors on the endothelium, which in turn activate endothelium nitric oxide synthase (eNOS) resulting in the production of NO from its precursor L-arginine. Subsequently, NO diffuses into adjacent smooth muscle cells causing smooth muscle relaxation via cyclic guanosine monophosphates' (cGMP) stimulation of sarcoplasmic reticulum Ca^+ uptake (Berne & Levy, 2001). Sodium nitroprusside and isosorbide dinitrate are endothelium independent, since they initiate smooth muscle relaxation directly via the cGMP pathway (Berne & Levy, 2001). L-NMMA is a specific eNOS antagonist resulting in inhibition of endothelial derived NO. By administering L-NMMA prior to subsequent infusions of ACh or throughout stepwise increases of an exercise stimulus, one can evaluate endothelium dependent vasodilation based on blood flow changes caused by pharmacological stimuli (Green et al., 2002). For example, by comparing ACh mediated blood flow to ACh stimulated blood flow with L-NMMA inhibition, a measurement of endothelium dependent blood flow is derived (Green et al., 2002). Although preferable due to its repeatability and precision, invasive methods using brachial intra-arterial catheterization are difficult to justify in some research settings.

Endothelial dependent and independent assessment of conduit arteries made with Ultrasound Doppler are also possible. Assessment of flow-mediated dilation method involves the application of ischemia to an extremity for an extended period (4 to 10 minutes), after which ultrasonography is used to image the artery of interest (Verma et al., 2003). The brachial artery is the most commonly used conduit artery. Flow-mediated dilation measures endothelial dependent dilation, although its specificity to NO release from the endothelium has been questioned (Betik, Luckham, & Hughson, 2004). Nonetheless, the mechanism is similar to ACh mediated NO release; however, shear-stress caused by blood flow, induces activation of eNOS in endothelial cells. Endothelial-independent dilation can be accessed by measurement of arterial diameter and flow after administration of a sublingual glyceryltrinitrate (GTN). GTN acts as a NO donor causing direct stimulation of the cyclic-GMP activated dilation of smooth muscle cells in conduit arteries.

1.4.2 Vascular endothelial function and exercise

Numerous reviews have summarized the available literature concerning the effect of physical activity on endothelial function (see Moyna and Thompson, 2004). Almost without exception, impaired (endothelial dependent dilation of less than 4%) or reduced endothelial function is improved with an aerobic exercise intervention. These findings have been observed in young healthy men both cross-sectionally (O'Sullivan, 2003), and following intervention studies (Clarkson et al., 1999; Green et al., 2002; Green, Cable, Fox, Rankin, & Taylor, 1994; Kingwell, Sherrard, Jennings, & Dart, 1997; O'Sullivan, 2003). Furthermore, increased endothelial function has been observed systemically even

when exercise was limited to the lower limb (Green et al., 2002). One exception to these observations was an intervention study performed in middle-aged participants which did not result in endothelial function improvements (Maiorana, O'Driscoll, Dembo et al., 2001). This equivocal finding was attributed to the lower intensity exercise stimulus or to the possibility that the participants had fully functional endothelia prior to exercise training (Maiorana, O'Driscoll, Dembo et al., 2001).

Similar improvements have been observed in populations exhibiting a decreased or dysfunctional endothelium with aerobic exercise training (Gokce et al., 2003; Gokce et al., 2002; Hambrecht et al., 1998; Hornig et al., 1996; Linke et al., 2001; Maiorana, O'Driscoll, Cheetham et al., 2001; Maiorana et al., 2000; Walsh, Bilsborough et al., 2003) and in cross-sectional studies in men of different ages (DeSouza et al., 2000; Taddei et al., 2000). However the systemic effects of lower limb exercise have been questioned in these populations. The diversity of these populations include patients with coronary artery disease (Gokce et al., 2002; Walsh, Bilsborough et al., 2003), chronic heart failure (Hornig et al., 1996; Linke et al., 2001; Maiorana et al., 2000), and the elderly with endothelial dysfunction (Taddei et al., 2000).

Although favorable effects of aerobic exercise training inundate the literature, little is known regarding the effect of resistance training on endothelial function independent of aerobic exercise. Studies to evaluate the combined effect of aerobic and resistance training have been conducted in patients suffering from chronic heart failure (Maiorana et al., 2000) and Type 2 diabetes (Maiorana, O'Driscoll, Cheetham et al., 2001). Maiorana and colleagues (2001, 2000) used a circuit-training type program in

which participants completed resistance training exercise of specific body parts (seven exercises) interspersed with 45s of cycling at 70 to 85% of peak heart rate. Results in both population cohorts showed significant increases in brachial artery flow-mediated dilation following training. Although this study included a resistance training component, the intensity (55% to 65% of 1RM) and duration (one set) was restricted thus limiting conclusions regarding the effect of resistance training on endothelial function. As well, the high intensity aerobic training could have accounted for the observed changes in endothelial function.

Observations of impaired endothelial function have also recently been shown following intense aerobic exercise training. Bergholm and colleagues (1999) first noted reduced endothelial-dependent dilation following three months of running. The intensity and duration were high at a frequency of four times per week at 70-80% of each subject's VO_{2max} for a period of 60 minutes. The apparent reductions of endothelium-dependent dilation were related to reduced antioxidant in the circulation and possibly to a reduced NO bioavailability (Bergholm et al., 1999). Although a more recent study did not observe impaired endothelial-dependent dilation with high-intensity training, they did not find a beneficial effect as compared to exercise training of a moderate intensity (Goto et al., 2003). These findings suggest a unique parabolic relationship between the exercise stimulus and endothelial-dependent dilation.

1.5 Summary and statement of purpose

The effects of resistance exercise training on structural and functional attributes of the cardiovascular system are controversial or non-existent. Throughout the literature

aerobic exercise training is advocated for its positive effects on cardiovascular health, thus suggesting potential beneficial effects for other exercise modalities, such as resistance training. However, cross-sectional data suggests reduced arterial compliance with resistance exercise training (Bertovic et al., 1999; Miyachi et al., 2003) and reduced endothelial function with high-intensity exercise training (Bergholm et al., 1999). In addition, controversy exists regarding the blood pressure lowering effect of resistance exercise training. Therefore, the purpose of the current study was to evaluate central and peripheral arterial compliance, resting blood pressure, and brachial endothelial function throughout a twelve-week resistance exercise training study in young healthy males.

CHAPTER 2

ARTERIAL COMPLIANCE, BRACHIAL ENDOTHELIAL FUNCTION AND BLOOD PRESSURE ADAPTATIONS TO RESISTANCE TRAINING IN YOUNG HEALTHY MALES

2.1 INTRODUCTION

The health of the arterial system can be characterized by measurements of its functional and its structural attributes. Arterial blood pressure has been identified as an independent risk factor in the establishment and progression of cardiovascular disease (Greenland et al., 2004), while reduced arterial compliance has also been implicated in the progression of coronary artery disease (Arnett et al., 1994; Hodes et al., 1995; Rowe, 1987). Endothelial dysfunction, which describes a conduit artery's inability to dilate in response to chemical or physical stimuli such as shear stress, has also been observed in various populations including those with coronary artery disease (Gokce et al., 2002) and chronic heart failure (Gokce et al., 2003).

Exercise training has been used in the treatment and prevention of cardiac events with good effectiveness, and the inclusion of resistance exercise training has only recently been included in cardiac rehabilitation programs. Recent studies into the vascular effects of resistance training have revealed some unexpected findings. Cross-sectional comparisons between sedentary and resistance trained individuals have established reduced whole-body arterial compliance (Bertovic et al., 1999), and augmented age-associated central artery stiffening in resistance trained athletes (Miyachi

et al., 2003). However, Bertovic and colleagues (1999) compared populations who had significantly different resting arterial blood pressures, while Miyachi and colleagues (2003) did not find differences of arterial stiffness in his young population of sedentary and resistance trained athletes. Cross-sectional studies are also limited due to their inherent shortcomings.

Therefore, the purpose of the current investigation was to evaluate the effects of twelve weeks of high-intensity whole-body resistance exercise training on central and peripheral arterial compliance, resting arterial blood pressure and brachial vascular endothelial function in a population of healthy young men.

2.2 METHODS

2.2.1 Participants

Twenty-eight young healthy males (Table 2.1) with an average age of 23 ± 3.9 y (mean ± SEM) participated in this study. All participants were physically active, yet had not participated in a structured resistance training protocol for at least 6 months prior to the beginning of testing. Exclusion criteria included clinical signs of heart disease, diabetes or traumatic limb injuries such as torn ligaments. The experimental protocol was approved by the McMaster University Medical Ethics Board and all participants provided informed consent prior to participating in the study.

Table 2.1 Participant characteristics (Mean ± SEM)

Age (years)	Weight (kg)	Height (m)	BMI (kg/m^2)
22.9 ± 3.9	82.6 ± 2.4	1.79 ± 0.01	25.8 ± 0.78

2.2.2 Training Protocol and Progression

Participants were required to undertake twelve weeks of whole-body resistance training designed to induce muscle hypertrophy. Using a three-day cycle, participants completed resistance training sessions at a frequency of 5 times per week. Each training session focused on a different muscle groups thus providing a whole-body regime while maintaining adequate rest between training days of the same body part. The exercises sessions were structured as follows:

Table 2.2 Specific exercises completed on specific days using a three-day cycle.

Session 1	**Session 2**	**Session 3**
Leg Exercises	**Pulling Exercises**	**Pushing Exercises**
Leg Press	Lat Pull Down	Shoulder press
Leg Curl	Wide row (seated)	Bench press
Leg Extension	Narrow row (seated)	Vertical bench press
Calf raise	Biceps curl	Triceps press down
	Rear flyes	Chest flyes

Sessions were conducted at the Pulse Gym located in the Ivor Wynne building on the McMaster University Campus. Sessions were limited to weekdays (Monday to Friday)

while during weekends (Saturday and Sunday) participants were instructed not to participate in other resistance type exercises. Participants who were aerobically active were asked to simply maintain their current aerobic activity levels, while those not participating in aerobic activity were instructed to simply abstain from such activities until after the completion of the resistance training program.

All participants completed an identical training progression. Prior to the start of training, participants completed a familiarization session on all equipment to be used. Training sessions lasted rough one hour depending on the number of sets and reprtitions required. Rest between exercises and sets was monitored and maintained at 2 minutes throughout training. One repetition maximum lifts (1RM) were performed on each piece of equipment on the first day of training.

2.2.2.1 One repetition maximum lifts

One repetition maximum lifts (1RM) were performed on each piece of equipment at four time points: prior to the initiation of training, following the 4th week, following the 8th week, and following the completion of the 12th week of training. 1RM testing was performed at each time point coordinating with their 3 day exercise cycle (Table 2.2). Upon entering the gym participants performed a warm-up of one set of between 10-15 repetitions at < 50% of their 1RM on the machine to be used for 1 RM testing. Following a rest period of at least 2 min, participants were instructed to complete one full repetition on the apparatus. If participants were successful in completing the repetition, then the resistance of the machine was increased incrementally. This procedure continued until the participant could no longer complete a full repetition (complete range of motion) as

judged by the investigator. Throughout testing a minimum of 2 min of rest were incorporated following a completed repetition. The goal was to determine the participants' 1RM within 4 attempts. Participants were verbally motivated and encouraged throughout the 1RM testing sessions.

2.2.2.2 Training sessions and progression

Participants were accompanied by a personal trainer or had a personal trainer available to them at all training sessions. Once the 1RM was determined, participants were required to complete all exercises for that specific exercise session at an intensity and frequency as listed for the appropriate week. Table 2.3 illustrates the training progression outlined for all participants. If a participant was completing more than the required repetitions yet was unable to increase their 1RM value, they were encouraged to increase the resistance of the machine according to the guidelines listed in Table 2.3. Rest between exercises and sets was maintained at 2 min with participants performing a warm-up set of 10-12 reps at less than 50% of their 1 RM prior to all exercises described previously.

Table 2.3 Progression of the resistance training program

Week	Number of Sets	Number of Repetitions	Participant Instructions
1-2	2	10-12	Focus on form
3-5	3	10-12	80% of 1RM
6-7	3	8-10	3rd set to failure 80% of 1RM
8-10	3	6-8	3rd set to failure, intensity > 80% of 1RM
11-12	3	5-6	3rd set to failure, intensity > 80% of 1RM

2.2.3 Testing Procedure and Data Collection

Assessment of arterial compliance, brachial endothelial function and resting blood pressure was conducted twice prior to the initiation of training, once during the seventh week of training, and once following the twelfth week of training. All testing procedures were conducted using an identical protocol and subject to the same control measures. At all testing sessions, participants were tested a minimum of 24 h following their last training session and at the same time of the day (within ~ 2 h). Participants were asked to abstain from nicotine and caffeine for at least twelve hours prior to testing. Participants were tested ~ 4 h postprandial after the consumption of 1 can (237 ml) of a commercially available meal replacement (BOOST® Drink, Mead Johnson & Company, Evansville, USA).

2.2.3.1 Resting Blood Pressure

Blood pressure was measured in the left brachial artery while participants were in the supine position. Participants were instrumented with an oscillometric automated blood pressure measurement device (model CBM-7000, Colin Medical Instruments, San Antonio, USA) and instructed to lie motionless for a period of ten minutes. Following this rest period, blood pressure measurements were obtained in triplicate at intervals of 2 minutes.

2.2.3.2 Arterial Compliance

Arterial compliance was measured at three sites on the non-dominant side. Synchronized measurements of arterial blood pressure and arterial diameter were used to assess arterial compliance in the carotid, brachial and femoral arteries. Beat by beat

changes in blood pressure were obtained in the radial, carotid and brachial arteries. Throughout testing continuous measurements of radial artery blood pressure were obtained using applanation tonometry (model CBM-7000, Colin Medical Instruments, San Antonio, USA) while at the carotid and brachial arteries, a pen-like device containing a high-fidelity transducer (model SPT-301, Millar Instruments Inc., Texas, USA) was held perpendicular to the vessel of interest to obtain a continuous blood pressure waveform. Carotid artery blood pressure was obtained in the right carotid artery of all participants while ultrasound images were obtained in the left carotid artery. Brachial artery blood pressure was acquired distal to the portion of the vessel imaged with ultrasound. Beat by beat changes in blood pressure at the femoral artery were estimated using applanation tonometry at the radial artery (model CBM-7000, Colin Medical Instruments, San Antonio, USA).

Images of the carotid, brachial and femoral arteries were obtained using B-Mode Ultrasound (model System FiVe, GE Medical Systems, USA). A 10 MHz linear array probe was positioned longitudinally to the vessel of interest. The carotid artery was imaged ~2 cm proximal to the bifurcation that divides the vessel into the external and internal carotid arteries, whereas the brachial artery was imaged ~3-5 cm proximal to the antecubital fossa. The common femoral artery was imaged ~2-4 cm proximal to the bifurcation that divides the vessel into the superficial and deep femoral arteries. Two video clips of one complete heart cycle were obtained and digitally stored for off-line analysis of diameter change. Participants were also instrumented with an electrocardiograph (model Cardiomatic MSC 7123, Medical Systems Corp, USA) for

simultaneous recording of R-R intervals. All physiological measurements were input into a data acquisition board (model ML795, ADInstruments, Colorado Springs, USA) for analogue to digital conversion and stored on a personal computer (IBM Netvista x86 compatible processor, White Plains, USA) using commercially available software (Chart 4.2, ADInstruments, Colorado Springs, USA). Analogue signals were sampled at a frequency of 200 Hz. The synchronization and alignment of digital video clips with continuous blood pressure measurements was accomplished by external trigger, which produced a 1V pulse. This pulse was initiated whenever a digital image was stored on the ultrasound machine and was recorded along with the continuous measurement of blood pressure in the data acquisition software (Chart 4.2) to be used to determine the time-point at which a digital image (heart cycle) was stored. Figure 2.1 illustrates this process:

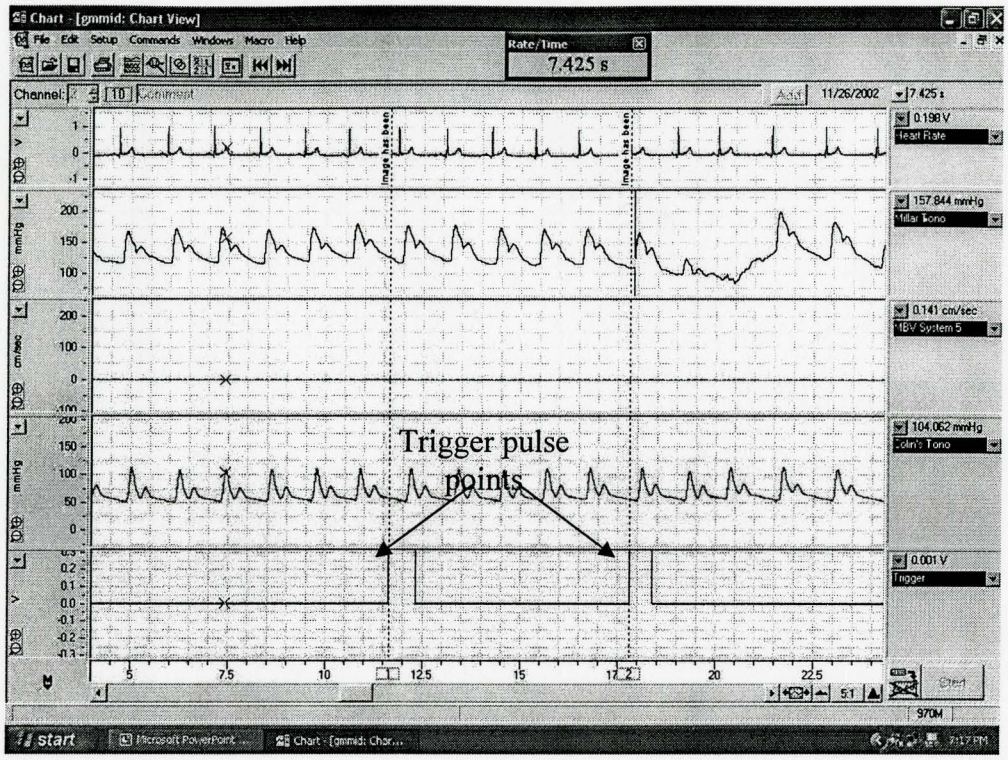

Figure 2.1 Screenshot of a typical Chart 4.2 data recording session. Arrows indicate the time points of Ultrasound digital image storage recorded in Channel 5 Channel 1 records a continuous ECG tracing, Channel 2 records continuous blood pressure at either the carotid of brachial arteries, Channel 3 records beat to beat measurements of mean blood velocity and Channel 4 records continuous blood pressure measured at the radial artery

2.2.3.3 Brachial Endothelial Function

Brachial vascular endothelial-dependent function was evaluated using a flow mediated dilation (FMD). A pneumatic cuff connected to a rapid inflation system (model E20 and AG101, Hokanson, Bellevue, USA) was placed around the forearm 2-4 cm distal to the antecubital fossa. The cuff was inflated to a pressure of at least 200 mmHg or 50 mmHg above SBP to ensure occlusion of the brachial artery Occlusion was maintained for a period of 4.5 min. A 10 MHz linear array Ultrasound probe was positioned ~3-5 cm proximal to the antecubital fossa to obtain a longitudinal image of the brachial artery A

continuous video recording of the brachial artery was obtained from 15 s prior to cuff deflation until 70 s following cuff deflation. In addition, a 16.7 s digital video clip was stored at 70 s following deflation. This digital video clip obtained digital images at a rate of 10/s from 53 to 70 s following cuff deflation. In parallel to the imaging of the brachial artery, mean blood velocity (MBV) was obtained using the duplex function of the previously described linear array probe. The duplex function of the Ultrasound is illustrated in Figure 2.2.

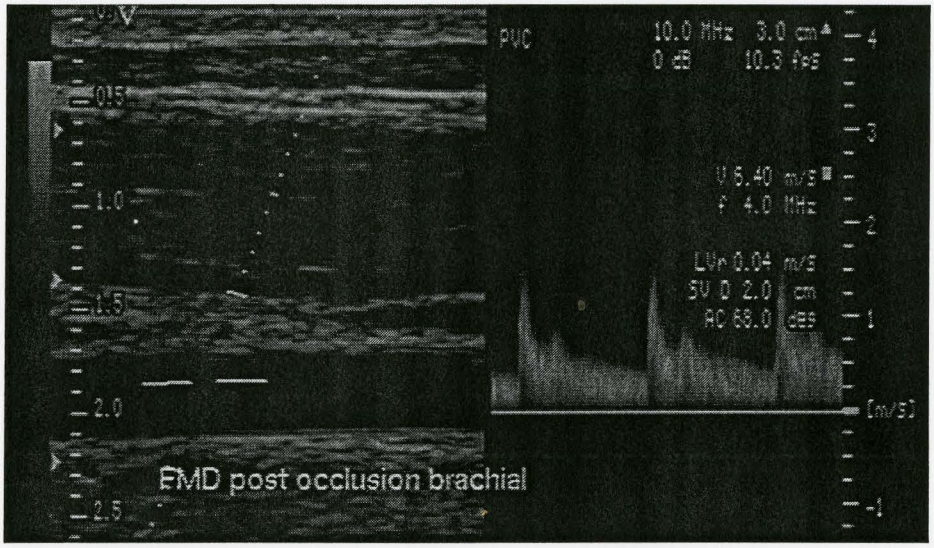

Figure 2.2 An example of the duplex function of the System FiVe Ultrasound Doppler Machine. The left portion of the diagram is a B-Mode display while the right side of the diagram illustrates the velocity profile obtained with pulse wave Doppler

Blood velocity was measured from 15 s prior to cuff release until 15 s following cuff release. All measurements of blood velocity were obtained at a pulse wave frequency of 4.0 MHz, using a velocity range gate of at least 500 cm/s, and a sample volume that enveloped the entire vessel beyond its walls. In addition, the insonation angle was

recorded for subsequent analysis of the raw audio signal. The following equation describes the Doppler equation that is used to determine red blood cell velocity:

$$f_d = f_t - f_r = (2v f_t \cos 0)/c$$

where f_d = frequency difference
f_t = transmitted frequency
f_r = received frequency
v = velocity
0 = angle of insonation
c = speed of sound in tissue

2.2.3.4 Blood Velocity

The raw audio signal corresponding to blood velocity was output from the Doppler ultrasound system into a transcranial Doppler system (model Neurovision 500M TCD, Multigon Industries, Yonkers, USA) running spectral analysis software. A fast Fourier transform (FFT) was applied to the raw audio signal to determine MBV continuously. Blood velocity was corrected for insonation angle, which was $\leq 68°$ for all measurements.

2.2.4 Data Analysis and Calculations

Digital images obtained with B-mode Ultrasound were converted to DICOM compressed JPEG stacked image files for further analysis of mean diameter, and Δ diameter using automated software (AMS II, Chalmers University of Technology, Göteborg, Sweden). Data files containing continuous blood pressure and MBV data were analyzed using Chart 4.2 software.

2.2.4.1 Resting blood pressure

Resting blood pressure was characterized using several different methods. SBP and DBP measurements were determined as the average of the oscillometric

measurements made in triplicate. Pulse Pressure (PP) was calculated using the following formula:

Equation –1- $PP = SBP - DBP$

where, PP is pulse pressure

DBP is diastolic blood pressure

SBP is systolic blood pressure

An average of this value obtained in triplicate was used for statistical analysis. MAP was calculated using the following formula:

Equation –2- $MAP = 1/3(PP) + DBP$

where, PP is pulse pressure

DBP is diastolic blood pressure

An average of this value obtained in triplicate was used for statistical analysis.

2.2.4.2 Mean Arterial Diameters

Resting carotid and brachial artery digital video clips were analyzed using an identical protocol. Two single heart cycle digital video clips (either brachial, carotid and femoral) were loaded and visualized on a personal computer (Pentium 4 2.66 GHz, clone) using specific image analysis software (AMS II). A clear portion of the image was chosen for automated analysis by the investigator. Regarding images obtained at the carotid artery, the region of interest (ROI) was established as ~2-3 cm proximal to the bifurcation of the carotid artery into internal and external branches, while the ROI of the brachial artery was merely kept consistent at all time-points within each subject. The investigator sized and positioned the ROI rectangle to encompass both near and far blood

vessel walls and initiated a command to permit the program to track diameter changes and mean diameter from leading edge to leading edge throughout subsequent frames of the digital video clip. Figure 2.3 illustrates the diameter vessel wall segments used for diameter measurements.

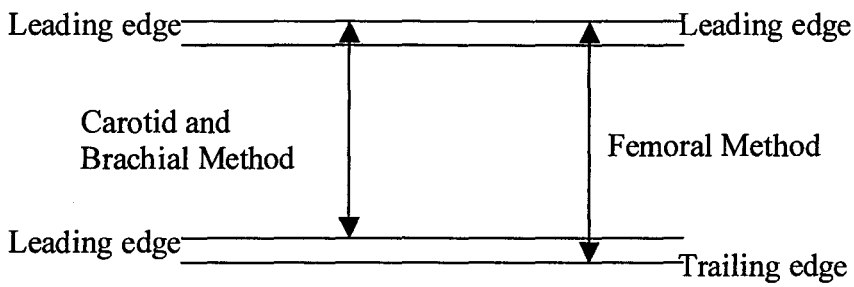

Figure 2.3 A schematic representation of the determination of vessel diameters in the carotid, brachial and femoral arteries. Carotid and brachial arteries are measured from leading to leading edge while femoral artery diameters are measured from leading edge to trailing edge.

The software program performed a minimum of 100 measurements of the artery diameter to obtain a mean arterial diameter for each frame of the digital video clip. To obtain a measurement of mean artery diameter for one heart cycle, an average was calculated from all but the last frame (since it was at the same time point as the first) of one video clip. Mean heart cycle diameters from the two video clips were subsequently averaged to obtain mean artery diameters for the carotid and brachial arteries. Femoral mean artery diameter was processed in the same manner; however, diameters were defined as leading edge to trailing edge since endothelial borders were not consistently visible in all images. Furthermore, diameters were consistently measured ~2-3 cm proximal to the bifurcation

of the common femoral artery that separates the vessel into deep and superficial branches at all time-points.

Figure 2.4 illustrates the automated arterial diameter analysis program (AMS II).

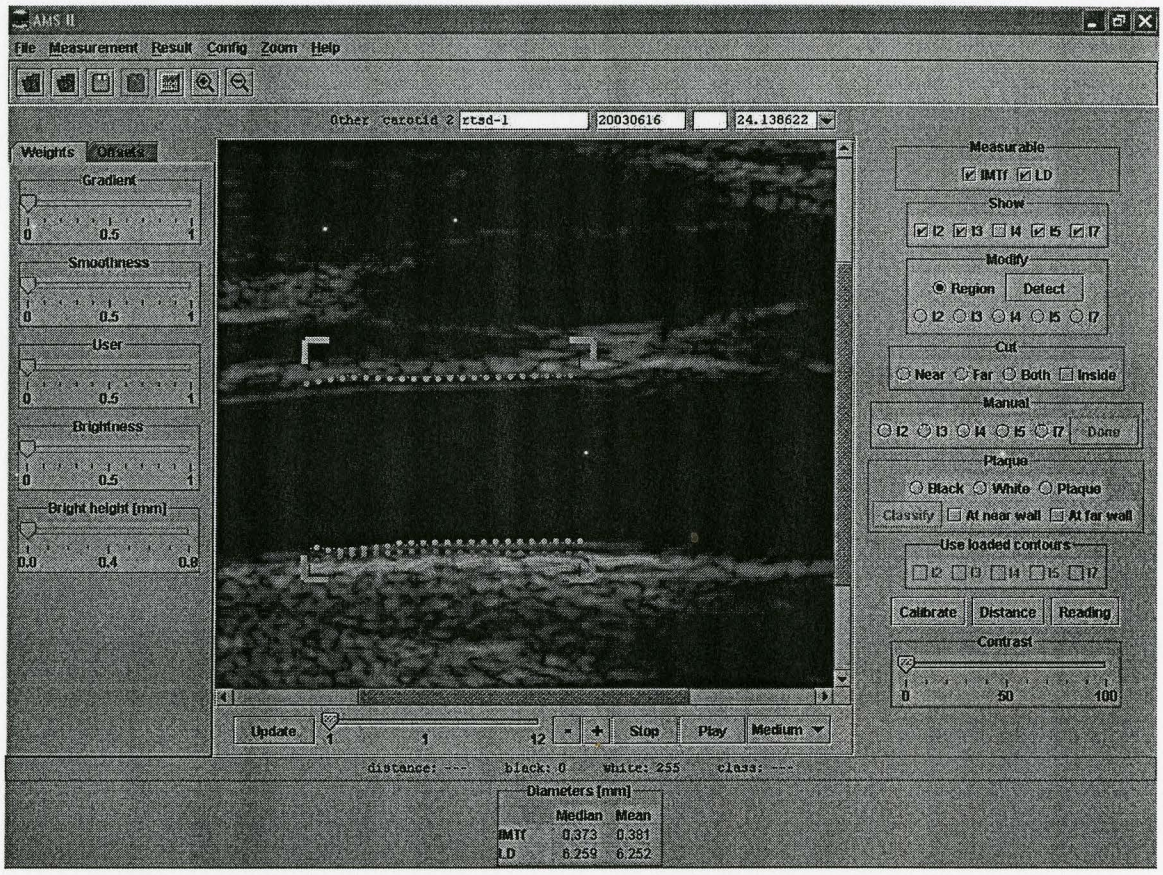

Figure 2.4 A diagram of the AMS II diameter analysis software. Turquoise angles encompass the region of interest determined by the investigator and green dotted lines are the automatically detected vessel walls.

2.2.4.3 Delta Diameters

Delta diameters for the carotid, brachial and femoral arteries were acquired in duplicate from two separate heart cycle video clips. The automated edge-detection software program determined mean arterial diameter of all frames of the video clip throughout the cardiac cycle as previously described. The maximal and minimal arterial diameters were used to determine arterial diameter change or delta diameter according to the following formula:

Equation –3- Δ Diameter = Maximal diameter – Minimum Diameter

2.2.4.4 Arterial tonometer PP

PP obtained in the vessels of interest (carotid and brachial) and subsequently used to calculate arterial compliance and stiffness index were acquired using the pen-like arterial tonometer (Millar) as previously described. Since this device is sensitive to manual hold-down pressure, these values required adjustment based on several assumptions. First, it was assumed both arterial DBP and mean arterial blood pressure are similar in all conduit arteries when an individual is in the supine position (Nichols et al., 1998). However, SBP is not similar in all conduit arteries thus requiring an adjustment of the signal obtained by the Millar. The mean and minimum signals obtained by the Millar were equated to the mean arterial and DBP obtained by the radial tonometer (Colin). Subsequently, the maximum value recorded by the Millar was used as an extrapolation point from which SBP was obtained in the vessel of interest. Finally, since DBP is assumed to be similar in all conduit arteries, this value maybe subtracted from the extrapolated SBP to obtain PP in the vessel of interest (Kelly et al., 1989). This procedure was performed at all time-points at which PP was needed for the calculation of

cross-sectional compliance and stiffness index values for either the carotid or brachial arteries.

Femoral artery PP was calculated as the difference between SBP and DBP obtained from radial arterial tonometry since the Millar tonometer was unable to obtain a signal at this artery due to its anatomical location.

2.2.4.5 Cross-Sectional Compliance

At the carotid, brachial and femoral arteries, two measurements of cross-sectional compliance and stiffness index were calculated from the PP and delta diameters previously described and were subsequently averaged. Cross-sectional compliance was calculated as follows (O'Rourke et al., 2002):

Equation –4-

$$CSC = \frac{\Delta \text{ Area}}{PP} = \frac{\pi r^2_{max} - \pi r^2_{min}}{PP} = \frac{\pi(d_{max}/2)^2 - \pi(d_{min}/2)^2}{PP}$$

where,
CSC = cross-sectional compliance
PP = pulse pressure
r = radius of the artery
d = diameter of the artery
max = maximal value
min = minimal value

2.2.4.6 Brachial FMD

Digital video acquired from 53 to 70 s following cuff deflation was used to determine maximal dilation of the brachial artery. Similar to measurements of mean arterial and delta diameters, an ROI was chosen by the investigator based on resting images previously analyzed. Thus, the ROI was located in the same area of the brachial

artery that was imaged for resting diameters. Measurements of mean end-diastolic arterial diameter were taken for all beats that made up the 16.7 s video clip. These end-diastolic diameters were then averaged and used to calculate relative FMD of the brachial artery. This value was calculated as follows (Corretti et al., 2002):

Equation –5-

$$FMD = \frac{d_{\text{end diastolic FMD}} - d_{\text{end diastolic rest}}}{d_{\text{end diastolic rest}}} \times 100\ \%$$

2.2.4.7 Post occlusion blood flow and shear rate

Blood velocity recorded following brachial occlusion was used to obtain two quantifications of post occlusion blood velocity. First, beat-by beat average blood velocity was determined as the area under the curve from R to R points on the simultaneously recorded ECG channel for insonation angle corrected continuous MBV measures. Peak MBV was defined as the highest single beat average blood velocity after exclusion of the first beat following cuff deflation. A ten second average post occlusion blood velocity was defined as the average blood velocity for ten seconds following cuff deflation excluding the first beat. These values were subsequently used to calculate peak blood flow, ten second average blood flow, peak walls shear rate and ten second average wall shear rate.

Blood flow was calculated using both the peak beat and ten second average methods alluded to in the previous section. The following equation was used to calculate these values at all time-point for all brachial endothelial-dependent dilation tests:

Equation –6-

$$FBF_{peak} = \pi(d/2)^2 \times BV_{peak} \times 60\ s$$

where, FBF is forearm blood flow
d is resting brachial diameter
BV is blood velocity

$$FBF_{10\text{-}s} = \pi(d/2)^2 \times BV_{10\text{-}s} \times 60\ s$$

where, FBF is forearm blood flow
d is resting brachial diameter
BV is blood velocity

Shear rates were calculated both as a peak beat and ten second average shear rate based on the blood velocity measurements described previously. The following equations were used:

Equation –7-

$$Shear_{peak} = \frac{4 \times BV_{peak}}{d_{mean}}$$

where, BV is blood velocity
d_{mean} is average heart cycle diameter

$$Shear_{10sec} = \frac{4 \times BV_{10\text{-}s}}{d_{mean}}$$

where, BV is blood velocity
d_{mean} is average heart cycle diameter

2.2.4.8 Relative endothelial dependent FMD

Endothelial dependent FMD was calculated for all time points according to the following formula:

Equation –8-

$$FMD = \frac{d_{FMD\ end\ diastolic} - d_{rest\ end\ diastolic}}{d_{rest\ end\ diastolic}} \times 100\%$$

where, d is diameter
FMD is flow mediated dilation

2.2.4.9 Normalized endothelial dependent FMD

Endothelial dependent FMD previously calculated, was normalized for the average shear rate experienced during the post occlusion reactive hyperaemic blood velocity. The following equation was used to calculate a normalized FMD of the brachial artery:

Equation –9- $$\text{Normalized FMD} = \frac{\text{FMD}}{\text{Shear}_{10\text{-s}}}$$

2.2.5 Statistics

All variables were analyzed using a repeated measure analysis of variance (ANOVA) owing to the three time points of measurement. When a significant main effect was noted, a Tukey HSD post hoc test was used for subsequent analysis. Significance for all analysis was set at $P \leq 0.05$. All values are presented as mean ± standard error of the mean (SEM).

2.3 RESULTS

2.3.1 Resting blood pressure

SBP did not change ($P > 0.05$) at any time-point throughout the training (Table 2.4, Figure 2.5a), however DBP increased significantly ($P = 0.022$) from mid to post training time points (Table 2.4, Figure 2.5b). MAP did not change at any time point ($P > 0.05$) (Table 2.4, Figure 2.5c), however PP decreased significantly ($P = 0.003$) from mid to post training time points (Table2.4, Figure 2.5d).

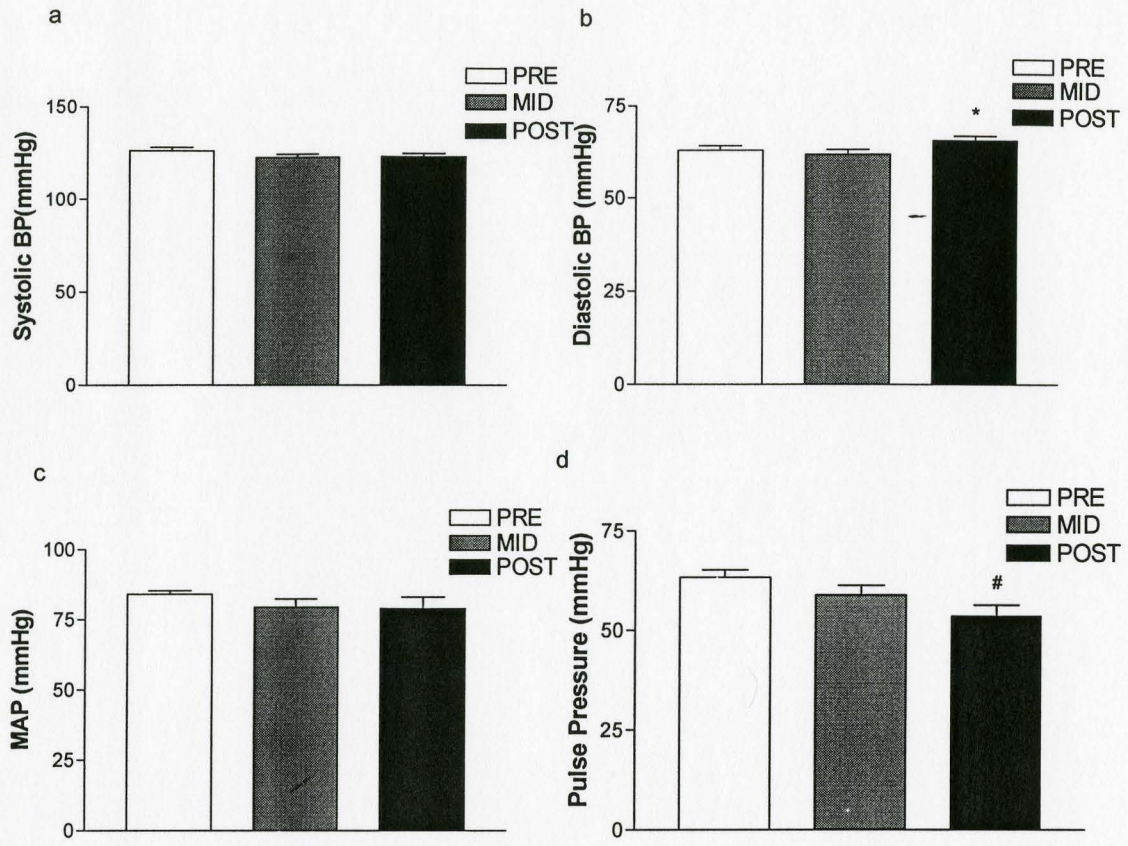

Figure 2.5 Resting blood pressure measurements pre, mid and post. a. illustrates systolic blood pressure (SBP), b. illustrates diastolic blood pressure (DBP), c. illustrates mean arterial pressure (MAP), d. illustrates pulse pressure (PP). #denotes significant difference from Pre values $P<0.05$, *denotes significant difference from mid values ($P<0.05$)

Table 2.4 Resting blood pressure at Pre, Mid and Post training

	Pre	Mid	Post
Systolic	126.3 ± 2.1	122.8 ± 1.7	123.0 ± 1.8
Diastolic	62.9 ± 1.2	61.8 ± 1.3	65.4 ± 1.2*
Mean Arterial Pressure	84.0 ± 1.3	79.4 ± 3.0	79.0 ± 4.0
Pulse Pressure	63.3 ± 1.9	59.0 ± 2.4	53.7 ± 2.8#

All values are mean ± SEM in mmHg, * denotes significant difference from Mid at $P<0.05$. # denotes significant difference from Pre at $P<0.05$.

2.3.2 Resting Arterial Diameter

Mean carotid and femoral artery diameters did not change ($P>0.05$) with training (Table 2.5, Figure 2.6a,c); however, the mean brachial artery diameter increased significantly ($P\leq0.01$) by the Mid time point and remained elevated at the Post training ($P\leq0.05$) (Table 2.5, Figure 2.6b) time point.

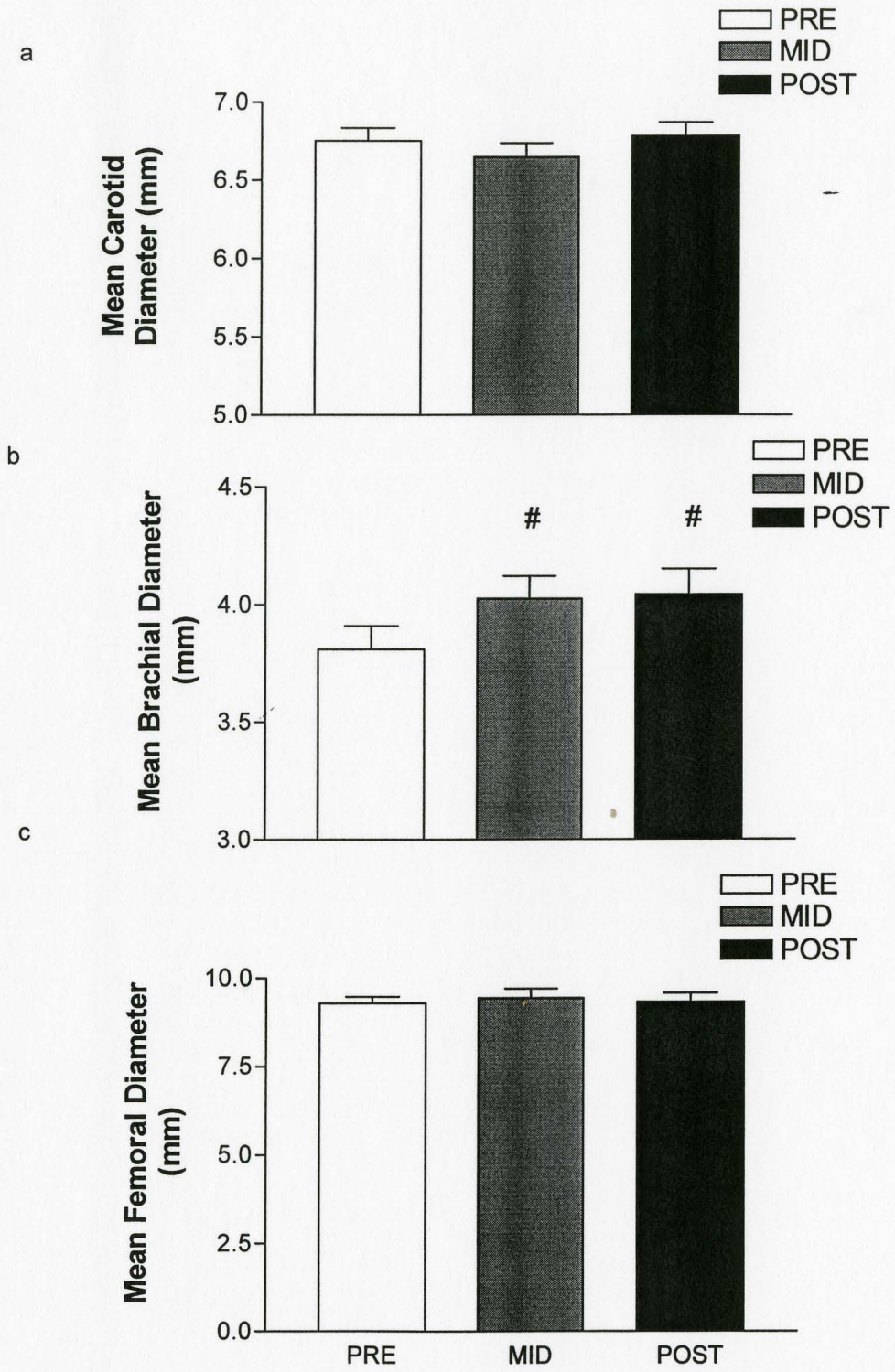

Figure 2.6 Mean arterial diameters at Pre, Mid and Post training. a illustrates mean carotid, b. illustrates mean brachial diameter, c. illustrates mean femoral diameter # denotes significant difference from Pre values ($P<0.05$).

Table 2.5 Resting mean arterial diameters Pre, Mid and Post training

	Pre	Mid	Post
Carotid	6.75 ± 0.08	6.65 ± 0.09	6.78 ± 0.09
Brachial	3.81 ± 0.10	4.03 ± 0.10#	4.04 ± 0.11#
Femoral	9.29 ± 0.18	9.43 ± 0.26	9.33 ± 0.24

All values are mean ± SEM in mm, # denotes significant difference from Pre at $P<0.05$

2.3.3 Cross-Sectional Compliance

Cross-sectional compliance (CSC) measured at the carotid and brachial arteries did not change significantly ($P>0.05$) at any time point throughout the training (Table 2.6, Figure 2.7a,b), however a reduction ($P=0.01$) in femoral CSC was apparent by the Mid training (Table 2.6, Figure 2.7c) time point and this reduction was still evident at Post training.

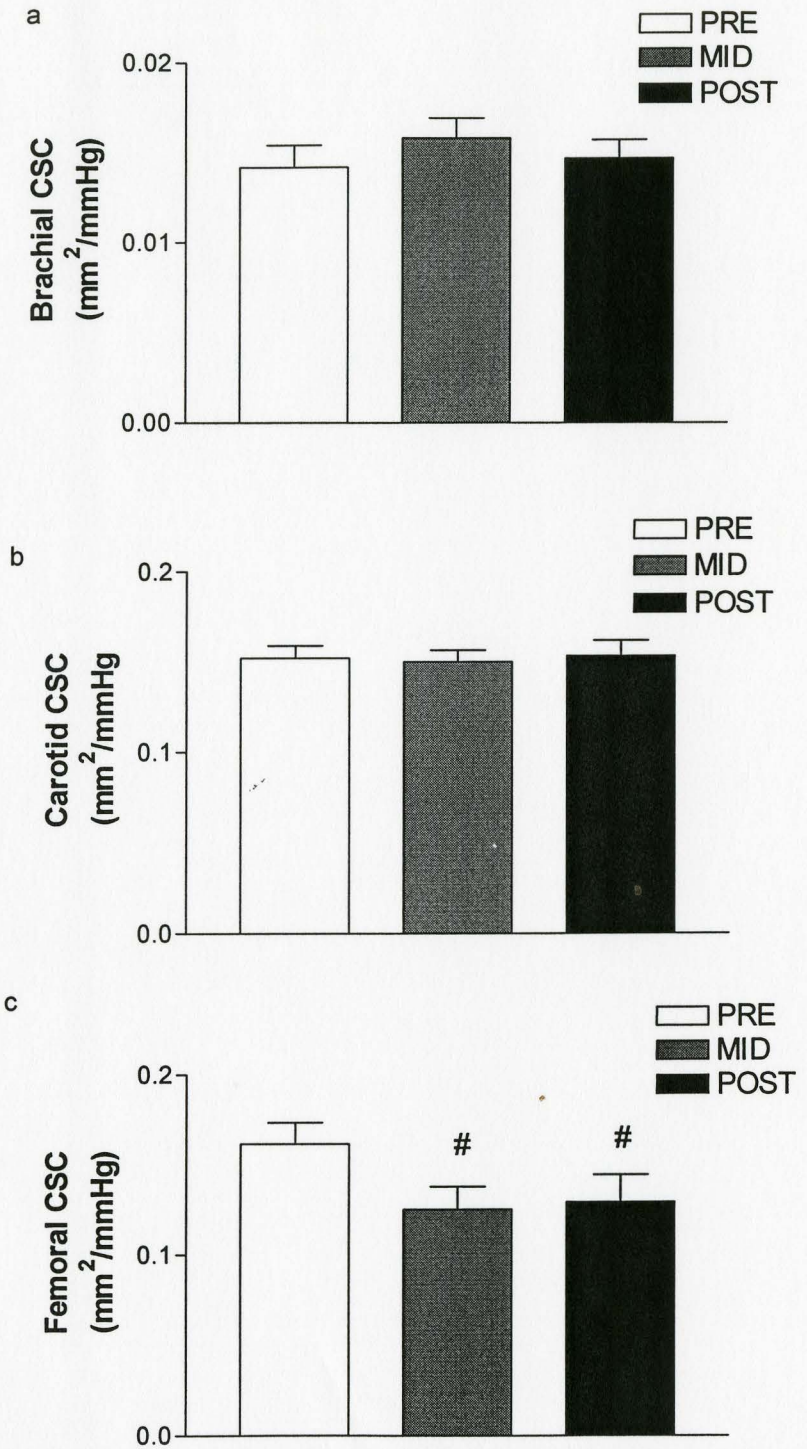

Figure 2.7 Cross-sectional compliance (CSC) at Pre Mid and Post training time points. a. illustrates carotid CSC, b. illustrates brachial CSC and c. illustrates femoral CSC. # denotes significant difference from Pre values ($P<0.05$).

Table 2.6 Resting cross-sectional compliance Pre, Mid and Post training

	Pre	Mid	Post
Carotid	0.152 ± 0.007	0.150 ± 0.007	0.153 ± 0.009
Brachial	0.014 ± 0.001	0.016 ± 0.001	0.015± 0.001
Femoral	0.162 ± 0.012	0.125 ± 0.013#	0.129 ± 0.015#

All values are mean ± SEM in $mm^2/mmHg$, # denotes significant difference from Pre at $P<0.05$

2.3.4 Brachial FMD responses

Peak beat (Table 2.7, Figure 2.8a) and 10-s average (Table 2.7, Figure 2.8b) blood flow following the 4.5 min of occlusion measured at the brachial artery was significantly ($P \leq 0.01$) elevated at the Mid training time point and remained elevated ($P \leq 0.05$) compared to Pre values at the Post training testing session.

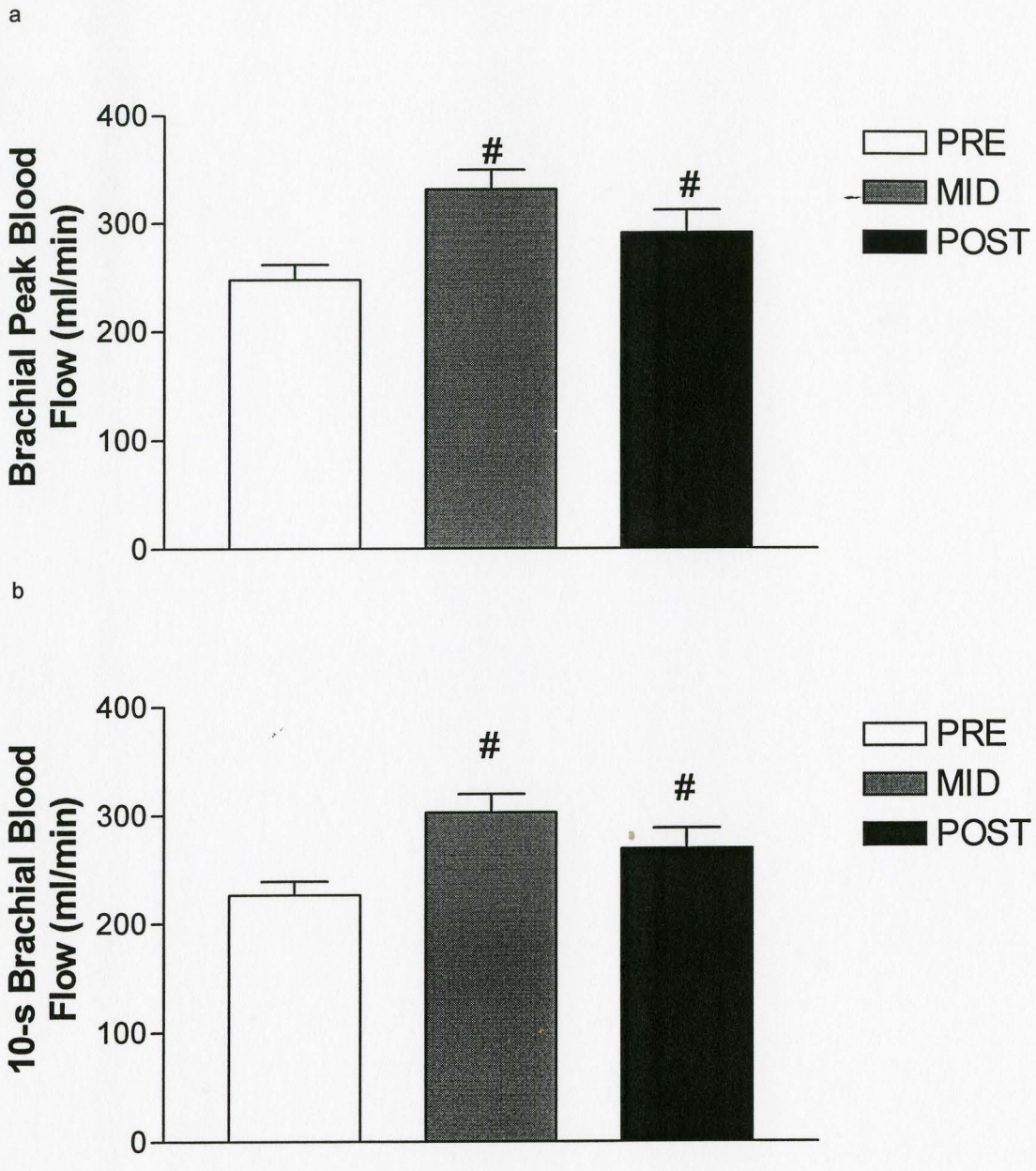

Figure 2.8 Brachial blood flow following 4.5 min of lower arm occlusion at Pre, Mid and Post training. a illustrates peak one beat blood flow while b. illustrates 10-s average blood flow. # denotes significant difference from Pre ($P<0.05$)

Table 2.7 Brachial flow mediated dilation responses Pre, Mid and Post training

	Pre	Mid	Post
Peak Brachial Blood flow (ml/min)	247.5 ± 14.0	331.1 ± 18.5#	290.5 ± 21.0#
10-s Average blood flow (ml/min)	226.4 ± 12.9	302.4 ± 17.5#	269.1 ± 18.9#
Peak shear rate (s^{-1})	38.6 ± 1.47	43.1 ± 1.87	39.2 ± 2.06
10-s average shear rate (s^{-1})	35.2 ± 1.4	39.0 ± 1.5	36.3 ± 1.8
Relative flow mediated dilation (%)	7.85 ± 0.8	8.86 ± 0.9	8.32 ± 0.8
Normalized flow mediated dilation (%/s^{-1})	0.236 ± 0.02	0.216 ± 0.02	0.27 ± 0.03

All values are mean ± SEM, # denotes significant difference from Pre values ($P<0.05$)

Peak beat (Table 2.7, Figure 2.9a) and 10-s average shear rates (Table 2.7, Figure 2.9b) in response to 4.5 min of forearm occlusion were not significantly difference ($P>0.05$) at any time point. Similar to shear rate measurements, relative FMD of the brachial artery was not altered ($P>0.05$) by training (Table 2.7, Figure 2.10a). In addition, when the relative FMD was normalized for mean wall shear rate (Table 2.7, Figure 2.10b), no significant differences ($P>0.05$) were noted.

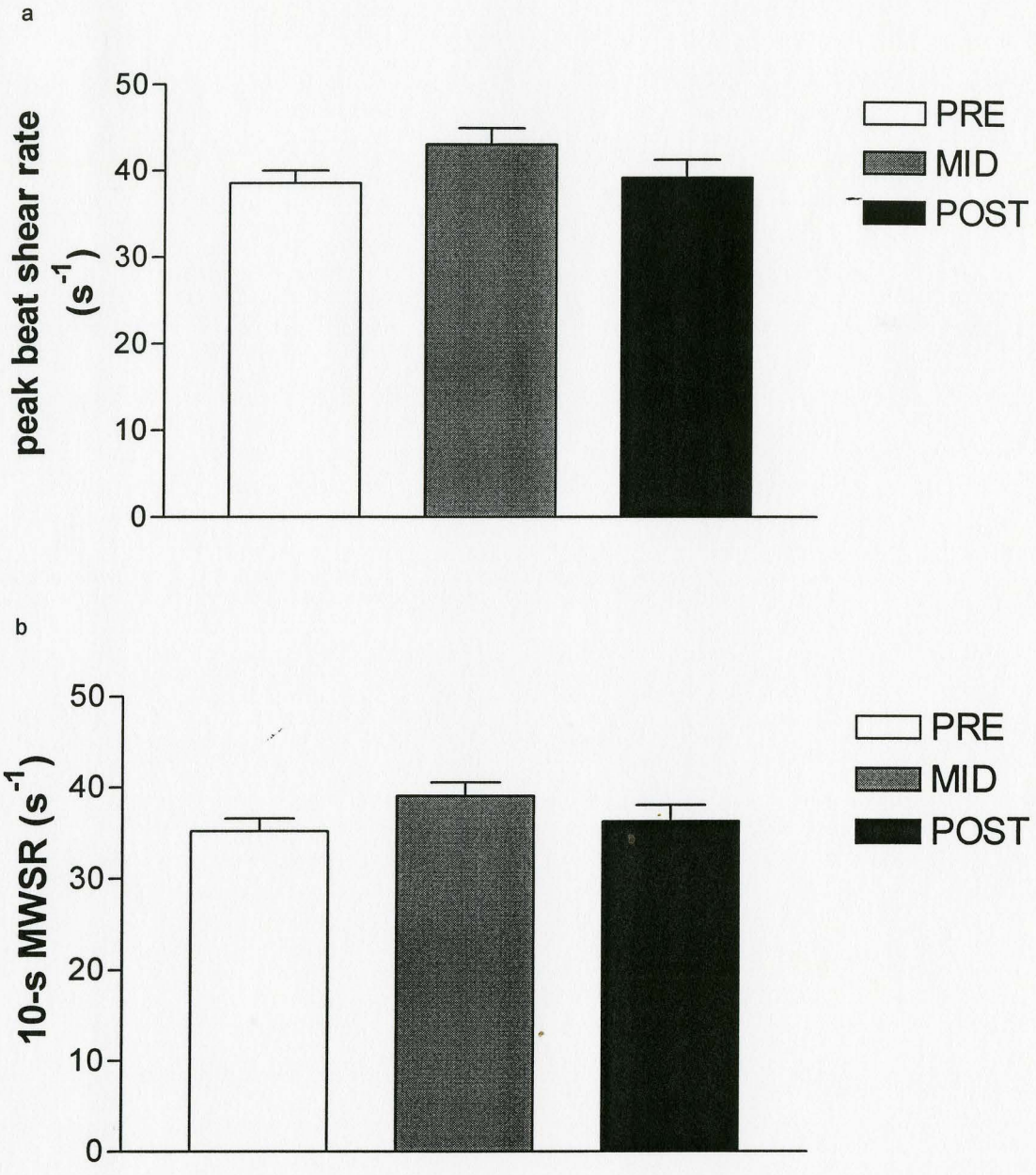

Figure 2.9 Peak beat and 10sec average wall shear rate following 4.5 min of forearm occlusion at Pre, Mid and Post training time points. a. illustrates peak beat shear rate while b. illustrates 10-s mean wall shear rate. No significant differences were noted at any time points.

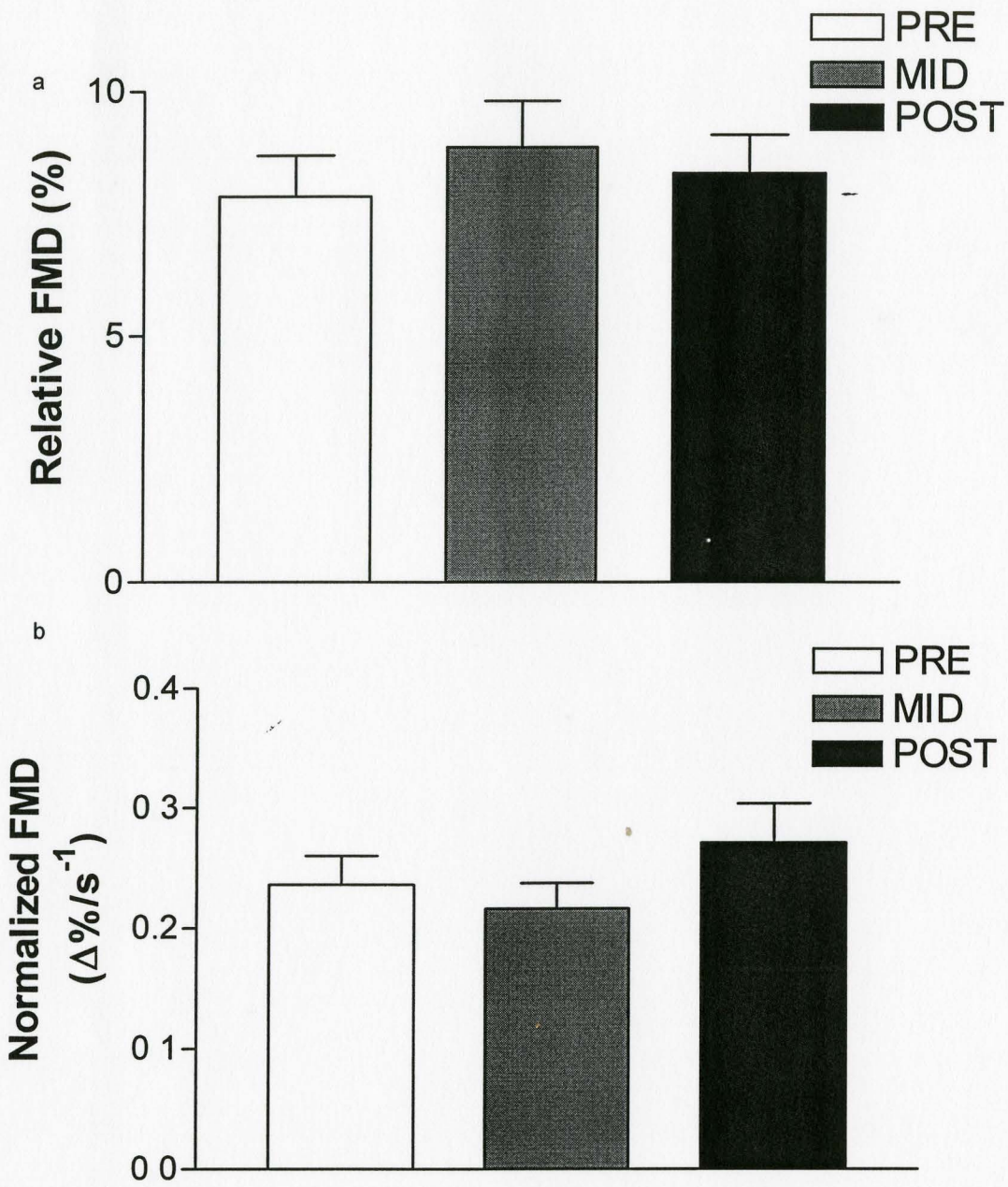

Figure 2.10 Relative and normalized brachial FMD at Pre, Mid and Post training time points. a. illustrates relative change in brachial artery diameter while b. illustrates the relative change in brachial artery diameter when normalized for 10-s mean wall shear rate. No significant differences were noted at any time point.

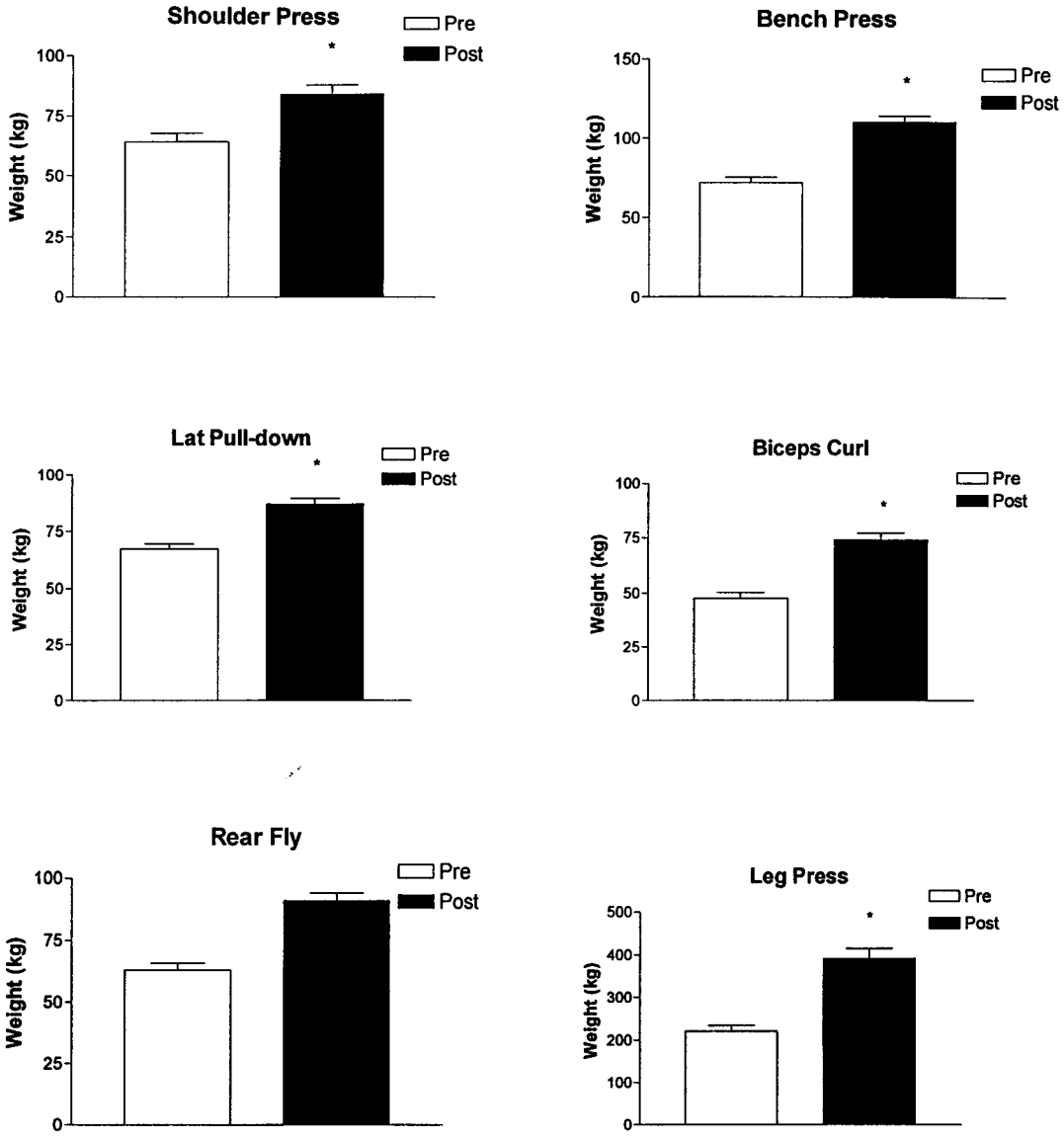

Figure 2.11 Representative one repetition maximum lifts prior to and following exercise training of various body parts. * Denotes a significant difference at a level of $p<0.05$.

2.3.5 One repetition maximum lifts and lean tissue gains

One repetition maximum performance was increased with resistance exercise training. Performance of shoulder press, bench press, lat pull-down, biceps curl, rear fly and double leg press were all significantly increased ($P \leq 0.05$) (Figure 2.11). Similar increases were noted in other muscle groups not listed or graphed. Lean tissue as

measured by DEXA showed a significant increase from Pre to Post training (Pre: 64106.1±1568.5 Post: 66410.1±8466.9 g; $P \leq 0.05$).

2.4 DISCUSSION

The purpose of this experiment was to determine the effects of twelve weeks of whole-body resistance training on resting arterial blood pressure, arterial compliance and brachial endothelial function in young healthy men. Alterations of resting PP, DBP, femoral artery compliance and resting brachial artery diameter were noted during this time and will be discussed in subsequent sections.

2.4.1 Resistance training and resting blood pressure

The primary findings related to resting blood pressure are a significant increase in DBP and a reduction of resting brachial PP with high-intensity resistance training. Otherwise no alterations of arterial blood pressure, measured in the brachial artery, were apparent. Alterations of DBP may not be of particular importance since differences were only apparent between the Mid and Post training time-points, and were not significantly altered compared to Pre training values. In contrast, the reduction of PP is an observation that has not, to our knowledge, been observed. Rather, Bertovic and colleagues (1999) observed an augmented PP both in the carotid and brachial arteries of their resistance trained group compared to sedentary controls. This elevated PP, however, was observed only in this study of cross-sectional design and not replicated by Miyachi and colleagues (2003).

The reduction of PP or augmentations of DBP may be due to a number of mechanisms including alterations of sympathetic flow to the renal or muscle systems, alterations of circulating vasoactive agents including Angiotensin II, vasopressin (AVP), catecholamines and endothelin-1, and endothelial vasodilator function.

Alterations of sympathetic flow to the renal system has been previously proposed as a possible mechanism responsible for reductions of resting blood pressure following resistance or isometric exercise training (Carter et al., 2003; Ray & Carrasco, 2000). However, direct evidence supporting this mechanism is lacking and will likely not be available in the near future due to measurement difficulties in humans. Muscle sympathetic nerve activity (MSNA) has been studied in resistance trained athletes (Sinoway, Rea, Mosher, Smith, & Mark, 1992) and following eight weeks of whole-body resistance training (Carter et al., 2003). Elevated MSNA levels in resistance trained athletes were noted (Sinoway et al., 1992) however resting arterial blood pressure was not significantly different from the sedentary control group who had relatively reduced levels of (MSNA). No elevation of MSNA was found following resistance exercise training in the longitudinal study by Carter and colleagues (2003). In contrast, Taylor and colleagues (2003) have shown increased heart rate variability with isometric handgrip training. This may indicate a more favorable balance between sympathetic and parasympathetic flow; however, isometric handgrip training is not dynamic and does not involve a large muscle mass as is the case with resistance exercise training.

Similarly, alterations of AVP or resting catecholamine levels with resistance exercise training have not been shown, however decreased plasma renin activity at rest

has been noted following aerobic exercise training (Geyssant et al., 1981). Endothelin-1 has recently been shown to decrease concomitantly with increases in basal circulating levels of NO products following exercise training (Maeda et al., 2001). A reduction of circulating endothelin-1 levels may contribute to lower total peripheral resistance and a subsequent reduction of resting blood pressure. These findings are difficult to relate to the current study because the exercise modality was aerobic rather than resistance exercise training.

Limitations of arterial blood pressure measurement may also contribute to the significant increases of DBP from Mid to Post training time-points found in the current study. Cuff size, acute smoking, recent physical activity, talking, recent ingestion of pressure substances (caffeine, sodium, etc.) and other factors influence arterial blood pressure (Pickering, 2002). Of these factors, the most likely mechanism to explain the decreased DBP at the Mid time-point involves recent physical activity. At the Mid time-point measurements may not have been preceded by adequate time following the last training session since they were taken at the same time of day as pre-testing yet the participants' exercise session the previous day may have been late in the day. This would likely result in an underestimation of blood pressure at this time point in particular, since upwards of 48 hours elapsed prior to post-training measurements (MacDonald, 2002).

Since there were no significant changes in assessments of endothelial function in the current study, one can only speculate that the previously described mechanisms may contribute to the observed alterations of resting blood pressure. Thus, further research

into the exact mechanism of altered arterial blood pressure is warranted through careful examination of the above-mentioned vasoactive substances.

2.4.2 Resistance training and resting arterial diameter

The primary finding of interest was the apparent increase of the brachial artery diameter with resistance training. This change was apparent at the Mid time-point and remained significantly elevated at the Post time-point. Interestingly, this is the first time conduit artery diameter increases have been measured and shown with resistance training either in cross-section or longitudinally studies. Similar changes have been noted with other exercise training protocols both longitudinally (Dinenno et al., 2001) and cross-sectionally (Abergel et al., 1998; Giannattasio & Mancia, 2002). The mechanism responsible for this change may be functional or structural.

Although the data do not permit insight into a structural or functional adaptation, the following mechanisms are likely involved if these changes are due to structural remodeling. First, during an acute bout of exercise limb blood flow increases according to the demand of the working skeletal muscle. Augmented shear stress experienced by the arterial endothelial lining causes release of NO via eNOS activation. Subsequent diffusion of nitric oxide to the underlying tissues (smooth muscle and adventitial layers) likely signals arterial remodeling. A study by Tronc and colleagues (1996), in which common carotid blood flow was augmented via a-v shunt for a period of 4 weeks showed that arterial diameter increases to a size that normalizes shear stress to pre-shunt levels (Tronc et al., 1996). NO is important in this process as illustrated in a recent study in which inhibition of eNOS via L-NAME eliminated the arterial remodeling effects of high

flow (Lloyd, Yang, & Terjung, 2001). This same pathway may also contribute to arterial remodeling between resistance training sessions due to repeated, exercise induced increases in basal forearm blood flow. With resistance exercise training the muscle involved in the exercise experiences damage prior to remodeling and hypertrophy. During this phase, oxygen demand may be increased above pre-exercise levels. Thus, increases in resting blood flow through the brachial artery to meet oxygen demand may induce an elevated shear stress and tonic increases of nitric oxide release in turn, stimulating arterial remodeling. Longitudinal and comparison studies support the idea of muscle hypertrophy or atrophy induced changes in resting arterial diameter.

Studies involving individuals with spinal cord injury are ideal for evaluating changes in arterial diameter with exercise training since atrophy of the artery occurs rapidly following injury (De Groot et al., 2003). Several studies by Nash and colleagues (1996, 1997) have shown that, with different types of electrically induced muscle stimulation training methods, the diameter of the common femoral arterial significantly increases. These changes are rapid, occurring within 12 weeks of training, and sizable with increases of ~ 25% (Nash et al., 1997). These data support the idea that arterial diameter changes occur in response to changes in muscle morphology (Nash et al., 1997; Nash, Montalvo, & Applegate, 1996). However, these data also support the premise that arterial enlargement may be caused by the acute increases in blood flow incurred during the electrically stimulated leg exercise (Nash et al., 1997; Nash et al., 1996).

Comparison studies in athletes have noted training induced changes in artery diameter; however, the precise location of this remodeling is seldom described.

Giannattasio and colleagues (1992) first noted a significantly increased radial artery diameter in the dominant arm of experienced hammer throwers. Similarly increased carotid artery diameters were noted in professional cyclists when compared to sedentary controls (Abergel et al., 1998); however, these two cross-sectional studies are limited. The first study did not include measurements of intima-media thickness, thus precluding information regarding the site of remodeling (Giannattasio et al., 1992). In the second study measurements of intima-media thickness were made; however, the carotid artery was examined rather than an artery of the exercising limb (i.e. common femoral artery) (Abergel et al., 1998). The sole longitudinal study to show enlargements of arterial diameter with exercise training attributed these changes to reductions of intima-media thickness (Dinenno et al., 2001). Further analysis of the current study dataset may reveal whether the changes of resting arterial diameter are limited to the intima-media layer or to vessel remodeling.

An increased arterial diameter may also be related to a chronic reduction of sympathetic activation; however, this mechanism is not likely in this study since reductions of DBP and SBP were not apparent with resistance training. Studies have shown reduced (Grassi, Seravalle, Calhoun, & Mancia, 1994), augmented (Sinoway et al., 1992) and equivocal (Somers, Leo, Shields, Clary, & Mark, 1992; Svedenhag, Wallin, Sundlof, & Henriksson, 1984) alteration of muscle sympathetic nerve activity (MSNA) with exercise training. Only two studies have examined the effects of resistance exercise training on MSNA. The first study examined the response of different athletes to handgrip exercise followed by circulatory arrest (ischemia of the exercising arm

immediately following exercise) (Sinoway et al., 1992). They observed baseline MSNA levels that were significantly higher in the resistance trained group compared to sedentary or endurance trained groups. The second study measured MSNA following eight weeks of whole-body resistance training and found no significant changes (Carter et al., 2003). Although the effect of resistance training on MSNA has not been extensively studied, support for the theory that this method of training reduces sympathetic tone is not extensive. Another measure used to give insight into the balance between sympathetic and parasympathetic tone is heart rate variability (HRV). Isometric handgrip training has been shown to increase HRV thus indicating reduced sympathetic tone and increased parasympathetic tone; however, whole-body resistance training is dynamic and thus quite different from isometric handgrip training (Taylor).

Increases in carotid and femoral artery diameters have been noted in athletes and active people (Abergel et al., 1998; Giannattasio et al., 1992; Schmidt-Trucksass et al., 1999) and following training of sedentary participants (Dinenno et al., 2001). In contrast, no significant changes in carotid or femoral arterial diameters with resistance exercise training were found in the current study. These apparent discrepancies are likely a result of the different exercise stimuli. For instance, the study by Abergel and colleagues (1992) noted increased carotid artery diameters in elite cyclists. In this population, the exercise stimulus is chronic in that 6 to 8 hours are devoted to training on a daily basis (Jeukendrup, 2002). This would amount to a significant shear stress stimulus even if shear rates were only 30-40% greater than resting levels as previously described (Hellstrom, Fischer-Colbrie, Wahlgren, & Jogestrand, 1996). Enlarged arteries

(common femoral) have been noted in endurance-trained athletes yet once again the flow stimulus as well as the frequency of stimulation (3-4 sessions during a two week period) in these studies was significantly greater than the likely flow stimulus in the current study. Limited evidence exists to support increases in carotid or femoral artery diameters with training, however future studies of greater duration and augmented exercise stimulus are needed to further establish this observation.

2.4.3 Resistance training and arterial compliance

The most interesting and unexpected finding regarding arterial compliance was a reduction at the femoral artery, which supports previous findings of Bertovic and colleagues (1999). However, contrary to previous studies, the carotid artery, a representative central artery, did not experience a reduction of its compliance with resistance training as predicted by Miyachi and colleagues (2003). Also of interest is the lack of a reduction at the other representative muscular artery, the brachial artery, which seems to contradict the change at the femoral artery. Numerous factors likely contribute to these findings including and not limited to alterations of MSNA, structural alterations of various vessels, muscle hypertrophy, sensitivity of the measurement method, the exercise-training stimulus and the time course required for adaptations of various vascular beds.

The present study is the first to observe reductions in compliance of the femoral artery with resistance exercise training, thus giving some support to Bertovic and colleagues (1999) who noted reductions of whole-body arterial compliance in resistance-trained athletes. Several mechanisms may contribute to this alteration. First, arterial

compliance is increased with acute applications of localized anesthesia at the brachial plexus or subarachnoid anesthesia which inhibited sympathetic activity at the radial and femoral arteries, respectively (Failla et al., 1999). Thus inversely, an increase of sympathetic tone may contribute to reduced arterial compliance. As mentioned previously, resistance trained individuals have shown increased sympathetic tone (Sinoway et al., 1992). The only study to follow alterations of MSNA with resistance exercise training using a longitudinal design showed no significant alterations; however, the training stimulus was rather short, lasting only eight weeks. As well, the training stimulus was substantially lower than the present study at 2-3 sessions per week using an identical training protocol throughout. In addition, Carter and colleagues (2003) showed an increase in MSNA when represented as a function of heart rate although it was not significant. One problem with linking reductions of femoral compliance to elevated sympathetic tone is that no reductions were noted at the other vessels of the body. Since sympathetic tone acutely affects radial artery compliance (Failla et al., 1999), significant reductions of brachial artery compliance would be expected if this were a contributor to altered compliance at the femoral artery. Thus, MSNA needs further attention as a mechanism of altered compliance with exercise training.

Alterations in femoral artery structure are likely responsible for the reductions of compliance noted in the current study. The acute high arterial pressure loads during resistance training, may cause damage to the vessel wall either at the level of the endothelium or adventitia possibly initiating a damage control response. As previously described, brachial blood pressure may reach values upwards of 320/250 mmHg during

double leg press (MacDougall et al., 1985), this would increase the tensile force experienced by the collagen fibres of the arterial wall (Matsuda et al., 1993) possibly resulting in an up regulation of collagen synthesis or cross-linking. With time, acute high levels of cyclic stress may alter the collagen/elastin ratio resulting in a reduction of resting arterial compliance. Alterations of aortic properties with endurance training have been shown in rat aorta with as little as sixteen weeks of exercise training (Matsuda et al., 1993) which give merit to expeditious alterations of vessel structure with exercise training. It is likely these pressure loads may be even greater in the femoral artery as a result of compressive forces.

Compression of arteries during resistance exercise may contribute to the stiffening of arteries. The time-course of these changes may differ from artery to artery possibly explaining the femoral artery stiffening without stiffening at the carotid or brachial arteries. The femoral artery is likely occluded and compressed by the external pressure of the muscles surrounding it periodically throughout an exercise session whereas, the carotid and brachial arteries are located more superficially and not surrounded by the same abundance of musculature. Since repetitions are of a high intensity, compressive forces may be high enough to cause damage to the adventitial layer resulting in a similar damage response as described previously with up regulation of collagen synthesis. This would not only decrease compliance, but also provide added stability to the artery that could resist the compressive force exerted by muscles during resistance exercise reducing the likelihood of occlusion. Further studies evaluating changes of arterial structure with resistance training are needed.

Arterial compliance measured at the carotid and brachial arteries did not change with resistance exercise training. Explanations for this unexpected finding may involve the effects of muscle hypertrophy, the time-course of vascular adaptations and the sensitivity of the measurement technique. The carotid and brachial arteries are easily accessible arteries located superficially. This permits blood pressure measurements to be acquired with relative ease. However, measurements of brachial artery diameter change measured throughout the cardiac cycle are not particularly accurate. The resolution of the ultrasound linear array probe combined with the relatively small change of diameter at the brachial artery throughout the cardiac cycle make estimates of compliance quite variable (Appendix C - brachial compliance CV 24.6%), thus reducing the chances of finding significant differences in a repeated measures design. The carotid artery is more easily imaged since the change in diameter throughout the heart cycle is relatively large compared to the brachial artery. However, the lack of a change in carotid or brachial artery compliance may also be influenced by muscle hypertrophy. Although difficult to support, hypertrophy of the musculature surrounding the femoral artery may reduce its distensibility without structural changes of the artery itself. This phenomenon may explain the discrepancies regarding no changes of artery compliance at the carotid artery since it is not surrounded by muscle tissue like the femoral artery.

The time-course of vascular adaptations may not be similar in all vessels contributing to the discrepant findings regarding arterial compliance changes with resistance exercise training. A recent study by Laughlin and colleagues (2004) noted divergent adaptations of various vessels following sprint training in rats. Particularly, the

sprint exercise training was expected to cause changes in vasodilatory capacity of the various arteries and arterioles feeding the white gastocnemius muscle (the predominant muscle exercised with sprint training). However, structural alterations were evident in some arterioles while functional alterations were noted in only a select few arterioles. The authors suggest a role for structural alterations affecting blood flow capacity with sprint training however the time-course of vascular adaptations may be different in the various arterioles supplying the working muscle (Laughlin, Woodman, Schrage, Gute, & Price, 2004). Thus, the adaptation to resistance training of the various conduit arteries studied in the current study may have different time-courses.

One final factor that may explain the apparent discrepant results regarding compliance reductions is the exercise-training stimulus. It is possible that structural changes of the femoral artery wall occur more rapidly than at the carotid artery. This could be related to the external compressive forces experienced exclusively at the femoral artery due to muscle contraction. The additional force may induce a greater damage response compared to the carotid artery, which does not experience external compressive forces. Also, compression of this artery during exercise causes high blood flow rates that may damage the endothelium. Thus, femoral artery compliance may decrease at a more rapid rate followed by reductions in central artery compliance like the carotid artery or proximal aorta. It is also possible intermittent high blood pressure is not enough to cause a damage response in the carotid artery of young healthy males. Some other trigger may need to be present such as advanced age, hormonal alterations, or nutritional insufficiencies or excesses for this stimulus to activate carotid artery stiffening.

Obviously further studies that control for these factors and apply a greater or more lengthy training stimulus are needed prior to definitive conclusions.

2.4.4 Resistance training and brachial endothelial function

Changes of brachial artery flow-mediated dilation did not occur with resistance exercise training; however, post-occlusion blood flow responses were increased as a result of training. More importantly, shear rates were unchanged with resistance exercise training when represented as either a peak or a 10-s mean. This further supports no change in flow-mediated dilation (brachial endothelial function) with a similar post-occlusion blood flow stimulus. Therefore, conduit artery endothelial function was unaltered with resistance exercise training.

The augmented blood flow response to 4.5 min of occlusion may be related to muscle hypertrophy, improved resistance vessel function or vascular remodeling. Although not measured, forearm hypertrophy is expected with resistance exercise training. This hypertrophied muscle mass would provide a greater metabolic stimulus for post-occlusion blood flow. As well, the larger brachial artery seen with resistance training would provide a greater conduit for blood flow following occlusion. This mechanism is likely even though it has not been assessed directly. Betik and colleagues (2004) did assess the effects of different ischemic stimuli on flow-mediated dilation and found significantly greater post-occlusion blood flow response when the occlusion cuff was positioned over the forearm as opposed to the wrist. This suggests a role for muscle mass in flow-mediated dilation procedures. Similar to a greater metabolic stimulus, greater resistance vessel function in reaction to the same ischemic stimulus at the level of the

arterioles may result in greater dilation of these arterioles. Greater dilation would result in lower resistance downstream of the conduit artery thus allowing for enhanced blood flow post ischemia. This type of exercise induced adaptation has been noted in the literature (Walsh, Yong et al., 2003). Walsh and colleagues (2003) noted improved resistance vessel function following combined resistance and aerobic exercise training in hypercholesterolaemic participants.

One final reason for the lack of an increase in flow-mediated dilation may be related to the function of the endothelium of the participants prior to resistance exercise training. It is possible the endothelium of these participants was already fully functional prior to training. Similar studies have noted this possibility (Maiorana, O'Driscoll, Dembo et al., 2001). Also, the training stimulus may not have been large enough or at a high enough frequency to cause endothelial function enhancements.

2.4.5 Limitations and future direction

The current investigation addresses many questions regarding the effects of resistance exercise training and vascular attributes; however, limitations include measurement techniques and technical limitations, population studied, and exercise modality.

The measurement technique used to acquire carotid, brachial and femoral artery compliance is one source of error. As previously mentioned, measurement of brachial artery diameter change varies considerably from day to day; however, adjustments of the testing protocol may eliminate this variability. As described in the Methods section, two heart cycle video clips were synchronized with simultaneous PP measurements. If

upwards of ten consecutive heart cycles were synchronized with corresponding PP measurements, the variability of this measurement would decrease substantially, likely improving the day-to-day variability of this measure. This same procedure would be applied to the carotid and femoral arteries.

Oscillometric, one-time, measurements of brachial arterial blood pressure are also of limited relevance since blood pressure fluctuates significantly throughout a typical day. Thus a more versatile measurement of arterial blood pressure may be appropriate. Measuring ambulatory blood pressure throughout a 24 hour period may be of augmented clinical importance than the measurements employed in the current study.

The flow-mediated dilation technique also exhibits some major limitations. One major limitation is the uncontrolled shear stimulus experienced by the vascular endothelium from day-to-day (Pyke, Dwyer, & Tschakovsky, 2004). The application of a constant shear stimulus has been recently suggested and a technique to do so has also been proposed (Pyke et al., 2004). Thus future studies would likely benefit from this improved technique. Also, measurements of forearm post-ischemia blood flow should be represented relative to tissue volume. Measurements of forearm volume may also give some indication of whether hypertrophy occurred with resistance training or whether augmented blood flow following resistance exercise training are merely a result of enhanced resistance vessel dilation to ischemia.

One must also observe the results of this study with caution. First, the exercise stimulus was extreme in that it was chosen to induce the greatest hypertrophy possible. Second, aerobic exercise training was controlled unlike in many rehabilitation and regular

exercise programs. Therefore the cardiovascular responses to resistance training are likely extreme and applicable to a specific population who routinely engages in high intensity resistance exercise training without an aerobic component to their program. Third, the population selected for this resistance exercise training intervention was young healthy males. Extrapolations of the results to other populations such as the elderly, females, or participants in cardiac rehabilitation are limited at best. Finally, the reduction of femoral artery compliance may not be a maladaptation meaning it provides a functional advantage for that particular vessel (Bertovic et al., 1999).

Future direction of this research involves further analysis of the collected data, future studies in humans, and the application of animal models to explore aspects not possible using humans. Further analysis of the collected data includes determining arterial compliance throughout the cardiac cycle. Thus, compliance could be represented as a curve from DBP to SBP. Subsequent comparisons between the compliance/pressure curves could be made throughout the time-course of the study. Further analysis of arterial remodeling would involve measurements of intima-media thickness. This measurement would allow the increase of arterial diameter to be attributed to the intima-media layer or to total arterial remodeling.

Future studies in humans could involve a similar exercise training protocol of a greater duration, different intensities, or various populations like females or the elderly. Numerous measurements that may be of interest include eNOS and SOD-1 protein expression either via vascular endothelial biopsy (as described by (Colombo et al., 2002)), FMD using a controlled shear stress stimulus (Pyke et al., 2004), and

measurements of arterial compliance without sympathetic influence (as described by (Giannattasio & Mancia, 2002).

Further studies involving animals would likely involve resistance exercise training in an attempt to cause muscle hypertrophy and alteration of arterial compliance. The advantage of the animal model would be the potential to evaluate aortic elastin, collagen, and calcium content. Also direct stress-strain relationships could be evaluated using aortic rings.

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Appendix A
ANOVA Tables

Systolic Blood Pressure – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	98	54	45	2.176	0.123

Diastolic Blood Pressure – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	90.3	54	22.3	4.051	0.022*

Mean Arterial Pressure – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	53.9	54	23.6	2.288	0.111

Pulse Pressure – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	174.5	54	28.0	6.232	0.003*

Carotid Cross-Sectional Compliance – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	0.000222	50	0.000787	0.2818	0.755

Brachial Cross-Sectional Compliance – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	0.000033	52	0.000026	1.2728	0.288

Femoral Cross-Sectional Compliance – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	0.01217	52	0.002392	5.0876	0.0095

Mean Carotid Artery Diameter– All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	0.113	52	0.041	2.757	0.0727

Mean Brachial Artery Diameter – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	0.456	52	0.050	9.178	0.00036

Mean Femoral Artery Diameter – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	0.135	52	0.401	0.337	0.715

Peak Brachial FMD Blood Flow – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	45402	52	2791	16.226	0.000003

10s Average Brachial FMD Blood Flow – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	37376	52	2205	16.953	0.000002

Peak Beat FMD Shear Rate– All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	171.3	52	69.5	2.4462	0.094785

10s Beat Average FMD Shear Rate – All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	105.0	52	53.3	1.972	0.1494

Relative Flow Mediated Dilation– All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	2.351	52	19.081	0.1232	0.884318

Normalized Flow Mediated Dilation– All Subjects						
Effect	df Effect	MS Effect	df Error	MS Error	F-ratio	p-level
TIME	2	0.01995	52	0.01105	1.8051	0.174619

Appendix B
Raw Data

RAW DATA: RESTING BLOOD PRESSURE

SYSTOLIC BLOOD PRESSURE (mmHg)

Subject	PRE	MID	POST
SA	119.3	112.3	105.0
AB	143.8	123.3	136.3
PB	151.3	124.3	129.7
FB	137.3	114.7	115.3
SD	128.3	134.0	128.3
ME	120.7	119.3	125.7
CF	122.7	124.3	120.3
NF	118.7	114.3	122.0
BG	117.3	123.0	122.3
BH	119.7	125.7	124.7
SH	142.7	118.7	145.3
MK	144.3	141.7	133.7
EK	117.3	117.0	111.3
PK	134.8	139.3	133.7
AL	123.0	118.0	118.7
JL	125.0	119.0	117.7
RM	136.3	128.0	118.3
RM2	125.3	120.0	124.0
WM	116.3	131.7	115.3
GM	115.0	117.3	106.7
DN	134.7	135.7	138.3
RP	115.0	119.0	126.3
RP2	110.7	104.0	113.7
JR	143.7	143.7	OUT
MS	113.7	119.0	126.0
MV	129.0	118.7	119.3
PW	123.3	123.7	132.0
JW	124.3	121.7	114.7
JW2	107.7	109.0	119.3
MEAN	**126.2**	**122.8**	**123.0**
SD	11.3	9.2	9.3
SEM	2.1	1.7	1.8

DIASTOLIC BLOOD PRESSURE (mmHg)

Subject	PRE	MID	POST
SA	63.3	57.0	55.0
AB	60.6	59.3	75.7
PB	76.7	67.7	70.7
FB	61.7	56.0	58.0
SD	57.7	71.3	71.0
ME	69.3	67.3	73.0
CF	57.7	55.3	63.3
NF	56.7	59.5	67.0
BG	52.3	60.5	54.7
BH	56.0	61.0	68.0
SH	62.3	51.0	70.3
MK	81.3	71.3	73.7
EK	56.3	53.8	59.3
PK	66.7	69.0	66.0
AL	66.3	59.7	67.3
JL	63.1	59.7	63.7
RM	67.7	62.7	59.3
RM2	61.3	60.0	67.7
WM	69.0	75.0	66.7
GM	63.0	59.7	54.7
DN	73.3	74.0	70.7
RP	60.7	67.7	70.3
RP2	65.7	58.0	60.7
JR	58.3	57.3	OUT
MS	60.0	56.3	63.7
MV	54.3	62.0	64.7
PW	64.7	71.0	79.0
JW	65.7	62.7	62.7
JW2	52.7	45.3	55.7
MEAN	**62.9**	**61.8**	**65.4**
SD	6.7	6.9	6.5
SEM	1.2	1.3	1.2

RAW DATA: RESTING BLOOD PRESSURE

MEAN ARTERIAL PRESSURE (mmHg)			
Subject	**PRE**	**MID**	**POST**
SA	82.0	75.4	71.7
AB	88.3	80.6	95.9
PB	101.6	86.6	90.3
FB	86.9	75.6	77.1
SD	81.2	92.2	90.1
ME	86.4	84.7	90.6
CF	79.3	78.3	82.3
NF	77.3	77.8	85.3
BG	74.0	81.3	77.2
BH	77.2	82.6	86.9
SH	89.1	73.6	95.3
MK	102.3	94.8	93.7
EK	76.7	74.8	76.7
PK	89.4	92.4	88.6
AL	85.2	79.1	84.4
JL	83.8	79.4	81.7
RM	90.6	84.4	79.0
RM2	82.7	80.0	86.4
WM	84.8	93.9	82.9
GM	80.3	78.9	72.0
DN	93.8	94.6	93.2
RP	78.8	84.8	89.0
RP2	80.7	73.3	78.3
JR	86.8	86.1	OUT
MS	77.9	77.2	84.4
MV	79.2	80.9	82.9
PW	84.2	88.6	96.7
JW	85.2	82.3	80.0
JW2	71.0	66.6	76.9
MEAN	**84.0**	**82.1**	**84.6**
SD	7.1	6.9	7.0
SEM	1.3	1.3	1.3

PULSE PRESSURE (mmHg)			
Subject	**PRE**	**MID**	**POST**
SA	56.0	55.3	50.0
AB	83.1	64.0	60.7
PB	74.7	56.7	59.0
FB	75.7	58.7	57.3
SD	70.7	62.7	57.3
ME	51.3	52.0	52.7
CF	65.0	69.0	57.0
NF	62.0	54.8	55.0
BG	65.0	62.5	67.7
BH	63.7	64.7	56.7
SH	80.3	67.7	75.0
MK	63.0	70.3	60.0
EK	61.0	63.3	52.0
PK	68.1	70.3	67.7
AL	56.7	58.3	51.3
JL	61.9	59.3	54.0
RM	68.7	65.3	59.0
RM2	64.0	60.0	56.3
WM	47.3	56.7	48.7
GM	52.0	57.7	52.0
DN	61.3	61.7	67.7
RP	54.3	51.3	56.0
RP2	45.0	46.0	53.0
JR	85.3	86.3	OUT
MS	53.7	62.7	62.3
MV	74.7	56.7	54.7
PW	58.7	52.7	53.0
JW	58.7	59.0	52.0
JW2	55.0	63.7	63.7
MEAN	**63.3**	**61.0**	**57.6**
SD	10.1	7.5	6.1
SEM	1.9	1.4	1.2

RAW DATA: CROSS-SECTIONAL COMPLIANCE (CSC)

CAROTID ARTERY (mm^2/mmHg)			
Subject	**PRE**	**MID**	**POST**
SA	0.132	0.148	0.130
AB	0.113	0.126	0.156
PB	0.136	0.147	0.226
FB	0.268	0.193	0.278
SD	0.124	0.162	0.128
ME	0.146	0.145	0.104
CF	0.158	0.147	0.155
NF	0.186	0.134	0.213
BG	0.172	0.133	0.131
BH	0.102	0.123	0.107
SH	0.165	0.189	0.136
MK	0.095	0.116	0.107
EK	0.162	0.123	0.173
PK	0.122	0.089	0.123
AL	0.177	0.232	0.217
JL	0.157	0.203	N/A
RM	0.163	0.149	0.209
RM2	0.130	0.132	0.174
WM	0.151	0.099	0.076
GM	0.120	0.167	0.182
DN	0.172	0.110	0.131
RP	0.115	0.137	0.130
RP2	0.127	0.172	0.121
JR	OUT	OUT	OUT
MS	0.175	0.120	0.121
MV	0.234	0.200	0.162
PW	0.151	N/A	0.145
JW	0.129	0.151	0.113
JW2	0.174	0.201	0.188
MEAN	**0.152**	**0.150**	**0.153**
SD	0.037	0.035	0.045
SEM	0.007	0.007	0.009

BRACHIAL ARTERY (mm^2/mmHg)			
Subject	**PRE**	**MID**	**POST**
SA	0.008	0.014	0.012
AB	0.015	0.013	0.015
PB	0.007	0.009	0.011
FB	0.014	0.019	0.006
SD	0.010	0.022	0.016
ME	0.016	0.026	0.007
CF	0.012	0.016	0.014
NF	0.019	0.012	0.017
BG	0.015	0.017	0.019
BH	0.014	0.008	0.010
SH	0.035	0.033	0.019
MK	0.008	0.017	0.021
EK	0.017	0.016	0.009
PK	0.013	0.013	0.016
AL	0.018	0.012	0.016
JL	0.031	0.017	N/A
RM	0.014	0.020	0.022
RM2	0.017	0.016	0.014
WM	0.017	0.010	0.015
GM	0.012	0.027	0.007
DN	0.013	0.006	0.012
RP	0.005	0.012	0.013
RP2	0.008	0.015	0.022
JR	OUT	OUT	OUT
MS	0.006	0.009	0.008
MV	0.009	0.017	0.019
PW	0.019	0.014	0.028
JW	0.015	0.017	0.010
JW2	0.012	0.014	0.018
MEAN	**0.014**	**0.016**	**0.015**
SD	0.007	0.006	0.005
SEM	0.001	0.001	0.001

RAW DATA: CROSS-SECTIONAL COMPLIANCE (CSC)

FEMORAL ARTERY (mm^2/mmHg)

Subject	PRE	MID	POST
SA	0.105	0.092	0.085
AB	0.056	0.094	0.066
PB	0.098	0.049	0.069
FB	0.311	0.395	0.403
SD	0.184	0.070	0.126
ME	0.130	0.065	0.160
CF	0.131	0.144	0.270
NF	0.219	0.221	0.103
BG	0.243	0.153	0.067
BH	0.160	0.119	0.067
SH	0.233	0.097	0.144
MK	0.140	0.143	0.138
EK	0.232	0.066	0.156
PK	0.084	0.097	0.083
AL	0.192	0.143	0.118
JL	0.122	0.105	N/A
RM	0.237	0.075	0.159
RM2	0.147	0.061	0.074
WM	0.164	0.123	0.049
GM	0.262	0.172	0.107
DN	0.145	0.152	0.046
RP	0.156	0.165	0.113
RP2	0.083	0.114	0.050
JR	OUT	OUT	OUT
MS	0.230	0.138	0.253
MV	0.104	0.120	0.163
PW	0.120	0.036	0.087
JW	0.127	0.106	0.113
JW2	0.141	0.189	0.220
MEAN	**0.163**	**0.125**	**0.129**
SD	0.061	0.068	0.079
SEM	0.012	0.013	0.015

RAW DATA: MEAN ARTERIAL DIAMETER

CAROTID ARTERY (mm)				BRACHIAL ARTERY (mm)			
Subject	**PRE**	**MID**	**POST**	**Subject**	**PRE**	**MID**	**POST**
SA	5.86	6.00	5.70	SA	2.86	3.42	3.26
AB	7.76	7.97	7.86	AB	5.04	4.66	4.76
PB	7.10	7.03	7.51	PB	3.10	2.95	2.92
FB	7.16	7.07	7.05	FB	3.92	4.25	N/A
SD	6.66	6.54	6.44	SD	3.65	3.92	4.25
ME	6.58	6.43	6.31	ME	3.56	3.78	3.69
CF	6.93	6.88	6.75	CF	3.94	4.38	3.83
NF	6.97	7.14	7.08	NF	3.74	3.84	4.44
BG	5.99	6.08	6.41	BG	3.28	3.93	3.59
BH	6.20	5.95	5.74	BH	3.07	3.09	3.35
SH	6.39	6.24	6.23	SH	4.14	4.30	4.60
MK	6.56	6.50	6.84	MK	3.97	3.99	5.08
EK	6.36	6.04	6.20	EK	3.70	4.09	4.12
PK	6.65	6.78	6.97	PK	3.55	4.10	4.23
AL	6.93	6.70	7.14	AL	3.75	3.74	3.68
JL	7.72	6.74	7.35	JL	4.84	5.10	4.83
RM	7.30	7.07	7.01	RM	4.75	4.68	4.95
RM2	7.08	6.73	6.89	RM2	3.99	4.20	4.22
WM	6.53	6.54	7.02	WM	4.01	3.66	3.92
GM	6.67	6.42	6.73	GM	3.78	4.28	4.02
DN	6.94	6.77	6.68	DN	3.89	4.02	3.85
RP	6.46	6.66	6.85	RP	3.50	3.96	3.77
RP2	6.67	6.70	6.83	RP2	3.72	3.99	4.11
JR	OUT	OUT	OUT	JR	OUT	OUT	OUT
MS	6.63	5.90	6.47	MS	2.92	3.06	3.07
MV	6.56	7.34	7.01	MV	3.92	3.81	3.98
PW	6.78	N/A	7.15	PW	4.12	4.91	4.44
JW	7.08	6.95	7.20	JW	4.56	4.65	4.74
JW2	6.52	6.33	6.46	JW2	3.45	3.97	3.51
MEAN	**6.75**	**6.65**	**6.78**	**MEAN**	**3.81**	**4.03**	**4.04**
SD	0.43	0.46	0.48	**SD**	0.53	0.51	0.56
SEM	0.08	0.09	0.09	**SEM**	0.10	0.10	0.11

RAW DATA: MEAN ARTERIAL DIAMETER

FEMORAL ARTERY (mm)

Subject	PRE	MID	POST
SA	6.20	6.86	6.57
AB	10.32	10.85	11.15
PB	7.37	6.32	6.73
FB	10.93	12.79	9.86
SD	9.96	10.59	10.88
ME	9.89	11.24	10.44
CF	10.06	10.54	10.00
NF	10.14	10.27	11.01
BG	8.77	7.64	8.84
BH	8.94	8.50	7.53
SH	8.70	9.56	8.32
MK	9.44	9.73	10.26
EK	8.64	7.78	9.06
PK	9.18	10.32	9.27
AL	9.04	9.46	8.94
JL	10.04	10.87	10.79
RM	9.34	9.21	9.69
RM2	10.12	9.54	9.64
WM	8.46	9.24	7.29
GM	10.22	10.44	9.35
DN	8.92	8.99	8.06
RP	8.96	8.56	8.89
RP2	9.19	8.96	10.28
JR	OUT	OUT	OUT
MS	9.33	7.87	9.38
MV	10.10	10.70	11.42
PW	10.29	8.37	9.43
JW	9.37	10.24	9.91
JW2	8.21	8.44	8.29
MEAN	**9.29**	**9.43**	**9.33**
SD	0.97	1.40	1.27
SEM	0.18	0.26	0.24

RAW DATA: POST OCCLUSION BLOOD FLOW

PEAK BEAT BRACHIAL BLOOD FLOW (ml/min)

Subject	PRE	MID	POST
SA	82.1	270.4	157.4
AB	226.1	402.0	507.5
PB	137.0	95.0	155.5
FB	189.9	329.1	156.6
SD	206.0	303.1	237.0
ME	278.4	309.2	207.9
CF	242.8	346.2	211.1
NF	264.0	274.9	260.7
BG	249.3	285.4	193.3
BH	145.2	171.9	140.2
SH	351.7	394.6	535.3
MK	273.9	416.7	430.4
EK	177.6	273.4	198.1
PK	236.6	364.0	316.0
AL	247.5	240.0	308.3
JL	422.1	564.0	N/A
RM	320.0	328.2	298.2
RM2	302.4	379.8	322.5
WM	318.0	459.2	375.7
GM	325.7	382.0	427.1
DN	281.8	329.0	318.6
RP	187.4	304.5	382.3
RP2	224.1	307.7	347.4
JR	OUT	OUT	OUT
MS	126.3	160.7	138.9
MV	268.4	297.2	232.5
PW	347.9	513.2	410.7
JW	271.1	401.1	324.8
JW2	227.0	367.4	249.2
MEAN	**247.5**	**331.1**	**290.5**
SD	74.3	97.7	109.2
SEM	14.0	18.5	21.0

10 SEC AVERAGE BLOOD FLOW (ml/min)

Subject	PRE	MID	POST
SA	71.8	230.8	143.9
AB	213.8	385.5	455.7
PB	122.1	84.5	144.7
FB	179.9	321.0	150.6
SD	192.4	272.3	223.7
ME	253.8	244.4	196.3
CF	226.0	328.4	198.1
NF	238.7	245.4	247.4
BG	227.1	261.2	179.4
BH	135.2	162.6	138.9
SH	324.7	374.6	494.6
MK	243.4	379.4	403.3
EK	164.9	252.2	187.4
PK	223.3	332.6	293.5
AL	228.9	225.3	292.4
JL	389.1	545.8	N/A
RM	283.4	310.6	294.8
RM2	271.2	359.2	308.1
WM	296.0	382.5	347.2
GM	303.8	325.0	360.2
DN	256.5	294.3	296.7
RP	176.2	266.3	345.7
RP2	190.8	294.2	322.4
JR	OUT	OUT	OUT
MS	116.8	143.8	129.7
MV	222.8	267.4	220.6
PW	325.9	464.3	381.7
JW	253.0	366.3	299.3
JW2	206.5	347.5	209.3
MEAN	**226.4**	**302.4**	**269.1**
SD	68.5	92.5	98.0
SEM	13.0	17.5	18.9

RAW DATA: POST OCCLUSION SHEAR RATES

PEAK BEAT BRACHIAL SHEAR RATE (S^{-1})

Subject	PRE	MID	POST
SA	29.7	57.5	38.4
AB	26.6	33.8	40.1
PB	39.5	31.3	53.1
FB	26.8	36.4	50.5
SD	35.9	42.8	26.3
ME	52.6	48.4	35.2
CF	33.6	34.9	32.0
NF	43.0	41.1	25.3
BG	53.8	47.0	35.4
BH	43.1	49.5	31.5
SH	42.2	42.2	46.6
MK	36.7	55.8	27.9
EK	30.1	33.9	24.0
PK	44.8	45.0	35.4
AL	40.2	38.9	52.7
JL	32.1	36.1	OUT
RM	25.7	27.1	20.9
RM2	40.3	43.5	36.5
WM	41.9	79.4	52.8
GM	51.2	41.5	55.8
DN	40.7	43.1	47.4
RP	37.0	41.7	60.6
RP2	36.7	41.3	42.4
JR	OUT	OUT	OUT
MS	43.2	47.7	40.7
MV	38.4	45.7	31.4
PW	42.5	36.8	39.8
JW	24.4	33.8	25.9
JW2	47.1	49.9	48.9
MEAN	**38.6**	**43.1**	**39.2**
SD	7.8	9.9	10.7
SEM	1.5	1.9	2.1

10 SEC AVERAGE SHEAR RATE (S^{-1})

Subject	PRE	MID	POST
SA	26.0	49.0	35.1
AB	25.1	32.4	36.0
PB	35.3	27.8	49.4
FB	25.3	35.5	48.6
SD	33.5	38.5	24.8
ME	48.0	38.3	33.2
CF	31.3	33.1	30.0
NF	38.9	36.7	24.0
BG	49.1	43.0	32.9
BH	40.2	46.8	31.2
SH	38.9	41.1	43.1
MK	32.5	50.8	26.2
EK	27.9	31.3	22.7
PK	42.2	40.1	32.8
AL	37.1	36.5	50.0
JL	29.6	34.9	OUT
RM	22.6	25.7	20.7
RM2	36.1	41.1	34.8
WM	39.0	66.2	48.8
GM	47.8	35.3	47.1
DN	37.0	38.5	44.1
RP	34.8	36.0	54.8
RP2	31.3	39.5	39.3
JR	OUT	OUT	OUT
MS	40.0	42.7	38.0
MV	31.9	41.1	37.0
PW	39.8	33.3	29.8
JW	22.7	30.8	23.8
JW2	42.8	47.2	41.1
MEAN	**35.2**	**39.1**	**36.3**
SD	7.3	7.9	9.4
SEM	1.4	1.5	1.8

RAW DATA: FLOW MEDIATED DILAITON RESPONSES

RELATIVE FLOW MEDIATED DILATION (%)

Subject	PRE	MID	POST
SA	7.2	3.1	9.4
AB	3.3	10.4	4.3
PB	10.6	17.9	7.4
FB	7.3	12.3	N/A
SD	23.3	18.5	7.4
ME	6.8	8.8	5.3
CF	7.1	1.4	6.3
NF	9.0	12.4	15.9
BG	5.6	4.7	11.8
BH	9.9	6.5	10.5
SH	16.0	8.6	2.4
MK	6.1	11.4	5.7
EK	4.0	6.8	2.4
PK	6.1	6.0	5.8
AL	10.6	6.6	8.7
JL	6.6	2.2	8.1
RM	5.2	12.3	4.0
RM2	5.8	7.7	3.3
WM	7.2	21.3	9.0
GM	5.6	2.2	6.6
DN	6.0	4.7	10.4
RP	12.3	10.5	10.5
RP2	12.8	8.6	13.1
JR	OUT	OUT	OUT
MS	8.3	7.1	2.6
MV	2.4	16.6	10.9
PW	6.2	5.4	9.7
JW	6.6	10.0	14.9
JW2	13.2	4.4	18.1
MEAN	**8.3**	**8.9**	**8.3**
SD	4.2	5.0	4.1
SEM	0.8	1.0	0.8

NORMALIZED FLOW MEDIATED DILATION (%/S^{-1})

Subject	PRE	MID	POST
SA	0.264	0.147	0.089
AB	0.130	0.101	0.288
PB	0.302	0.382	0.362
FB	0.284	0.205	0.252
SD	0.696	0.607	0.745
ME	0.138	0.177	0.265
CF	0.231	0.216	0.045
NF	0.237	0.246	0.516
BG	0.115	0.130	0.143
BH	0.233	0.212	0.208
SH	0.422	0.390	0.198
MK	0.191	0.119	0.434
EK	0.147	0.129	0.297
PK	0.142	0.152	0.182
AL	0.276	0.290	0.133
JL	0.217	0.188	OUT
RM	0.222	0.203	0.597
RM2	0.162	0.141	0.221
WM	0.100	0.109	0.436
GM	0.122	0.158	0.047
DN	0.162	0.156	0.108
RP	0.354	0.342	0.191
RP2	0.428	0.325	0.218
JR	OUT	OUT	OUT
MS	0.210	0.195	0.186
MV	0.083	0.058	0.448
PW	0.155	0.185	0.182
JW	0.284	0.213	0.420
JW2	0.309	0.280	0.107
MEAN	**0.236**	**0.216**	**0.271**
SD	0.126	0.112	0.169
SEM	0.024	0.021	0.033

Appendix C
Coefficients of Variation

Coefficient of Variation of Mean artery diameters

Subject	Carotid Artery	Brachial Artery	Femoral Artery
SA	5.1	3.9	4.7
PB	1.3	6.4	20.1
FB	0.9	3.9	4.8
SD	0.3	1.1	6.9
ME	1.7	5.0	13.5
CF	2.4	2.5	1.0
NF	0.2	1.4	4.5
BG	7.9	4.6	16.1
BH	1.9	2.1	1.7
SH	0.9	2.2	1.7
MK	0.4	5.5	5.8
EK	5.7	3.9	11.5
PK	0.8	4.3	No data
AL	3.1	3.0	10.5
JL	2.1	5.3	No data
RM	0.2	7.0	16.6
RM2	0.6	0.5	4.7
WM	1.3	0.4	No data
GM	1.1	1.0	5.1
DN	3.5	1.0	7.9
RP	4.2	1.7	9.9
RP2	1.5	0.6	3.7
MS	2.5	0.8	2.9
MV	5.8	0.8	4.4
PW	1.6	2.3	3.7
JW	4.9	3.4	1.6
JW2	0.9	1.3	6.9
MEAN CV	2.3	2.8	7.1

Coefficent of Variation of Cross-Sectional Compliance

Subject	Carotid Artery	Brachial Artery	Femoral Artery
SA	9.3	4.8	68.3–
PB	12.8	1.2	69.4
FB	26.7	22.6	28.5
SD	1.0	21.2	40.5
ME	6.3	28.0	11.0
CF	10.6	20.8	27.0
NF	41.3	7.3	9.3
BG	36.0	No data	26.8
BH	20.4	28.3	14.1
SH	2.0	64.4	61.6
MK	37.2	23.6	14.9
EK	35.1	55.8	2.0
PK	25.5	17.0	99.0
AL	13.4	2.9	41.4
JL	4.5	87.1	66.8
RM	15.0	60.4	94.0
RM2	8.8	7.4	34.4
WM	No data	No data	12.5
GM	34.8	4.8	22.8
DN	2.7	20.1	107.7
RP	30.0	2.8	31.1
RP2	17.9	6.4	10.9
MS	11.2	12.2	6.1
MV	No data	34.6	38.0
PW	7.1	6.3	15.7
JW	18.3	22.0	4.8
JW2	13.1	52.6	37.6
MEAN CV	17.6	24.6	36.9

Coefficient of Variation of Brachial FMD Parameters

Subject	Brachial Peak Flow	Brachial 10s Average	% FMD Brachial
SA	6.45	3.60	no data
PB	4.94	2.34	14.62
FB	5.15	6.98	47.77
SD	2.83	5.09	21.68
ME	6.31	5.40	60.56
CF	14.22	12.57	46.68
NF	5.66	11.55	8.78
BG	23.48	19.84	25.64
BH	30.59	35.04	66.34
SH	11.89	7.71	17.17
MK	24.36	30.03	21.73
EK	8.73	2.69	2.03
PK	8.09	9.39	79.61
AL	12.67	9.04	52.89
JL	9.89	11.15	44.33
RM	1.13	11.13	84.37
RM2	2.04	3.64	53.70
WM	0.24	5.01	no data
GM	22.11	22.17	30.40
DN	6.79	6.16	3.81
RP	7.08	5.55	20.98
RP2	43.85	38.60	14.16
MS	6.63	4.98	21.76
MV	5.11	12.83	no data
PW	12.87	9.97	14.04
JW	3.30	5.42	83.61
JW2	1.33	2.68	15.55
MEAN CV	10.66	11.13	35.51

Appendix D
Calibration of the System FiVe Doppler Ultrasound Blood Velocity Measurements

INTRODUCTION

The FMD technique requires a measurement of blood velocity and blood flow to determine the shear stimulus responsible for dilation of the blood vessel being evaluated. Recently, Doppler Ultrasound has been widely used for quantifying blood velocity in conduit arteries since it is relatively accurate and non-invasive (Radegran, 1997; Shoemaker, Pozeg, & Hughson, 1996). Unfortunately, the accuracy of blood flow measurement relies on some major assumptions that can significantly impact its reliability and reproducibility. The following equation describes the Doppler effect and the specifically how it is used to determine arterial blood velocity in tissues:

$$f_d = f_t - f_r = (2v f_t \cos 0)/c$$

where f_d = frequency difference
f_t = transmitted frequency
f_r = received frequency
v = velocity
0 = angle of insonation
c = speed of sound in tissue

The most influential component of this equation is the angle of insonation. This determinant of blood velocity may vary considerably both between and within the same subject and testing dates. Thus, accurate measurements of blood velocity and the subsequent calculation of blood flow need adjustment/correction based on the angle of insonation. Many Doppler systems automatically correct for angle of insonation to allow mean velocity can be manually estimated using internal calibrations for small segments of blood flow however, continuous determination of MBV requires external spectral analysis and calibration.

Therefore the subsequent sections describe the methods involved in obtaining analyzing and correcting the Doppler velocity signal from a GE System FiVE Doppler Ultrasound to obtain a relatively accurate and reproducible measurement of blood velocity at a number of insonation angles typically found during human investigations.

METHODS

Equipment Set-up

The Ultrasound probe (linear array of 5 or 10 Mhz) was immersed in water and positioned longitudinal to a translucent tube of known internal diameter using a stereotactic clamp as illustrated (figure 1). The tube was attached to an adjustable pulsatile pump system (Masterflex Model 77250-62, Cole-Parmer Instrument Company, Illinois, USA), which generated pulsatile blood flow over a variety of flow rates. Red blood cells were simulated using a colloid solution of water and corn starch providing a medium for the backscattering of the Ultrasound Doppler signal. The angle of insonation was adjusted based on B-Mode ultrasound using the sample volume envelop and angle correction utility inherent to the System Five. When changes in angle were needed, manual adjustments of the probe were made and subsequently confirmed using the angle correction utility.

The raw audio signal corresponding to blood velocity was output from the Doppler ultrasound system into a transcranial Doppler system (model Neurovision 500M TCD, Multigon Industries, Yonkers, USA) running spectral analysis software. A fast Fourier transform (FFT) was applied to the raw audio signal to determine MBV continuously. The mean velocity signal was output from the transcranial Doppler system

into an analogue to digital data acquisition board and recorded on a personal computer running Chart 4.2 data recording software for offline analysis. MBV was sampled at a rate of greater than 200Hz.

Various parameters of the System FiVe Doppler ultrasound system affect the frequency shift detected and subsequently output as part of the raw audio signal. These parameters include: 1) the transmitted Doppler frequency, 2) sample volume, 3) high pass filter (Low velocity reject), 4) Doppler Probe selected (5 or 10 Mhz), and 5) the velocity range. The transcranial Doppler system used to perform the FFT and output MBV also may affect the voltage obtained by Chart 4.2. Thus, a standard velocity range was selected which was large enough to encompass the physiological range of blood velocities on both the System FiVe and transcranial Doppler systems. This standard velocity range was maintained throughout the calibration protocol. Other parameters maintained throughout the calibration protocol include the sample volume (9.0mm-maximum envelop), and high pass filter (LVreject). Doppler probe, Doppler transmitted frequency and the angle of insonation were adjusted according to the following figure to ensure thorough calibration at all possible System FiVe settings:

Doppler Probe	Doppler Transmitted Frequency	Angles of Insonation
5 Mhz	4.0 Mhz	56°-68° at 2° intervals
	4.4 Mhz	56°-68° at 2° intervals
	5.0 Mhz	56°-68° at 2° intervals
	5.7 Mhz	56°-68° at 2° intervals
10 Mhz	4.0 Mhz	56°-68° at 2° intervals

4.4 Mhz	56°-68° at 2° intervals
5.0 Mhz	56°-68° at 2° intervals
5.7 Mhz	56°-68° at 2° intervals

Calibration trial

Two trials at each setting combination of probe, transmitted frequency and angle were completed. The pulsatile pump system was attached to the 6.01 mm tube that was aligned longitudinal to the linear array probe (either 5 or 10 Mhz). Eight pump speeds were selected ranging from low flow rates of 0 ml/min to greater than 1200 ml/min to encompass most physiological flow rates of the brachial and carotid arteries. The pump speed was adjusted using the analogue dial corresponding to incremental increases in pump rate. Pump speeds used for calibration were from 0 to 3.5 at 0.5 increments of the dial. Once steady flow was apparent a measurement of mean voltage was collected for a 30sec period, at each pump speed using Chart 4.2 software. This procedure was repeated at each pump speed in sequence as mentioned previously. During the measurement of mean voltage, flow that had passed through the pump was diverted into a graduated cylinder and collected for a period of one minute. This collected sample provided a flow rate, which was used to calculate MBV for the corresponding mean voltage signal already obtained.

The flow collected during each pump speed was used to calculate MBV using the following equation:

$$MBV = \frac{MBF}{CSA}$$

$$= \frac{MBF}{(6.01mm/2)^2 * \pi}$$

where, MBV is mean blood velocity
MBF is mean blood flow
CSA is cross-sectional area

A regression of the MBV values and the corresponding mean voltages were made from the data of the two trials at each setting. Thus, a regression equation was obtained for each combination of probe, transmitted Doppler frequency and angle of insonation. These regressions were subsequently used to adjust any measurements of MBV collected using Chart 4.2 from the System FiVe Doppler ultrasound machine.

RESULTS

Sample trial results

The following data illustrates a group of values obtained during two different trials at a specific probe, transmitted Doppler frequency and angle of insonation. The regression line has been calculated and displayed in (figure 3) at represents the relation between mean voltage and MBV.

Table 2 Raw data for a set of trials using a 5Mhz probe at a transmitted frequency of 5.7Mhz and an angle of insonation of 64°.

Pump Speed (arbitrary units)	Flow (ml/min)	Velocity (cm/sec)	Mean Voltage (mV)
Trial 1			
0	0	0	0.4996
0.5	60	3.525	0.5347
1.0	195	11.456	0.6284
1.5	328	19.27	0.7289
2.0	470	27.61	0.8156
2.5	683	40.126	.9539
3.0	880	51.7	1.083
3.5	1040	61.10	1.192

Trial 2			
0	0	0	0.4996
0.5	60	3.525	0.5343
1.0	195	11.456	0.6288
1.5	330	19.387	0.7293
2.0	465	27.319	0.8233
2.5	668	39.245	0.9560
3.0	870	51.11	1.080
3.5	1040	61.10	1.186

5 Mhz Probe 64 degrees Freq 5.7Mhz

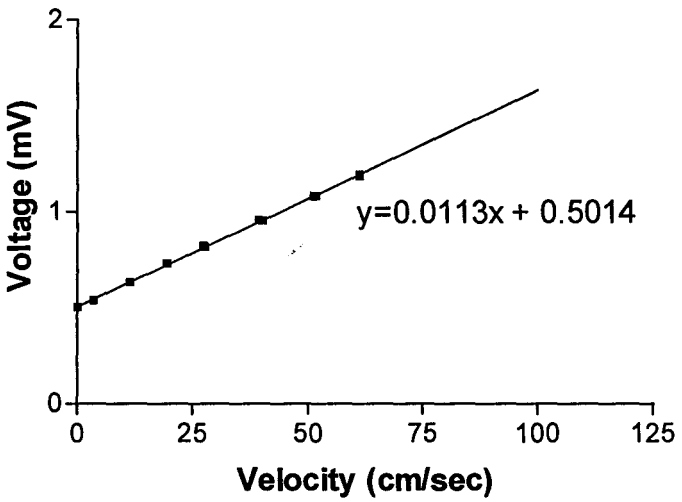

Figure 1 Regression graph of mean voltage against MBV. Equation of regression is inset.

Similar regression lines were determined for each set of parameters as listed previously.

DISCUSSION

The primary finding regarding the relation between MBV and the mean output voltage is that this relationship is linear. Therefore, a linear regression equation is adequate when adjusting mean voltages to MBV when using different $\bar{D}$oppler parameters. This is further supported by the r^2 value of the regression which is 0.9992 or greater at all different parameter combinations.