EXERCISE AND VASCULAR STIFFNESS IN COARCTATION OF THE AORTA

THE ACUTE EFFECTS OF MODERATE INTENSITY EXERCISE ON VASCULAR STIFFNESS IN CHILDREN WITH REPAIRED COARCTATION OF THE AORTA

By

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A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree

Master of Science

McMaster University

MASTER OF SCIENCE (2009) **McMaster University**
(Kinesiology) **Hamilton, Ontario**

TITLE: The acute effects of moderate intensity exercise on vascular stiffness in children with repaired coarctation of the aorta

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NUMBER OF PAGES: xiii, 144

ABSTRACT

Some individuals with coarctation of the aorta (CoA) have impaired cardiac and vascular structure and function, despite surgical intervention. Exercise training has been shown to improve cardiovascular structure and function in individuals with acquired heart disease; however, little information exists to inform exercise prescription in individuals with congenital heart abnormalities. Nine children with CoA (7 males, age: 12 ± 3 y) and 9 age and sex matched controls (7 males, age: 11 ± 3 y) completed a 20 minute bout of leg and arm cycling on two separate days at workloads which elicited exercising heart rates which were 50% above resting heart rate. Central arterial stiffness was measured using both carotid distensibility and pulse wave velocity (PWV) before exercise and at 5 and 15 minutes post exercise. At the same time points, upper limb and lower limb arterial stiffness were assessed using PWV. At rest prior to exercise, the CoA group had larger carotid lumen diameters in comparison to controls ($p<0.05$). Carotid distensibility was not different between the groups at any time point ($p>0.05$) and did not change in response to either arm or leg exercise ($p>0.05$). Central PWV was elevated at 5 minutes post arm cycling exercise (main effect for time, $p<0.05$) but was not different between groups ($p>0.05$). Central PWV was reduced at 5 and 15 minutes post leg cycling exercise in CoA and did not change in the controls. Non-exercised limb stiffness did not change with arm or leg exercise in either group ($p>0.05$). Stiffness decreased in the exercised limb following arm exercise ($p<0.05$) but not leg exercise ($p>0.05$). There was a significant group difference for slower PWV in the upper limb with arm and leg exercise in repaired CoA group in comparison to controls ($p<0.05$). Our findings indicate

that in contrast to previous reports, children with successfully repaired CoA may not be predisposed to increased arterial stiffness in the large conduit arteries proximal to the coarctation. Furthermore, this group of children with a successful repair of CoA had similar vascular responses to moderate intensity exercise as healthy age and sex matched controls and higher intensity exercise challenges may be needed to reveal divergent vascular responses in these groups.

ACKNOWLEDGEMENTS

There are many people who have been instrumental in the completion of this thesis. First and foremost, I would like to express my gratitude to my supervisor Dr. Maureen MacDonald. Thank you for your continuous guidance, support, and patience throughout this process. I feel fortunate to have worked in your laboratory and to have been given such a unique and interesting project. I appreciate the work you have done on all aspects of my thesis and the knowledge you have bestowed upon me. I admire your ability to balance both a successful laboratory and family.

This project would not have been conducted without the cooperation of Pediatric Cardiologist Dr. Rejane Dillenburg. Dr. Dillenburg, I am so appreciative that you took such a keen interest in this research. Thank you for all the time you took out of your already busy schedule to be in the laboratory for testing, even when it meant coming in on weekends. It was wonderful getting to know you during this time.

To my committee members, Drs. Neil McCartney and Brian Timmons, thank you for the insights you provided on my project. Dr. Timmons, thank you for the opportunity to be involved with the preschool research.

I would like to acknowledge the Exercise and Metabolism Research Group; especially members of the Vascular Dynamics Laboratory. Drs. Mark Rakobowchuk and Kyra Pyke, thank you for teaching me the techniques employed in the lab as well as developing my knowledge of the vascular system. Phil Millar, I am appreciative of the time you put into helping decipher my data. The direction and input you provided were essential in the successful completion of my thesis. Katharine Currie, thank you for your

assistance with the start-up of my study and for your insight into my results (and making sure I was always taken care of). Lisa Cotie, thank you for stepping in when needed for data collection. Kaitlin Hammel, I am appreciative of the time, effort, and diligence you put into the data collection, analysis, and editing aspects of my thesis. And finally, Todd Prior, thank you for keeping everything together in the lab; especially the magical ultrasound fixes.

I would also like to acknowledge the Pediatric Cardiology unit at McMaster Children's Hospital, specifically Jane MacKenzie for assistance with patient selection and Annette Page for conducting the echocardiograms on the control participants. I am also very grateful to the participants and their families for taking the time to be involved in this study.

To my wonderful roommates – Emma, Paula, and Vanessa – these last few years would not have been the same without you. Your company on the late work nights was comforting, although not always productive. And finally, I am forever indebted to my family for their unconditional love and support throughout this degree and all of my endeavours.

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BMI	Body mass index
CoA	Coarctation of the aorta
CSA	Cross sectional area
DBP	Diastolic blood pressure
ECG	Electrocardiography
IMT	Intima-media thickness
LD	Lumen diameter
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
PP	Pulse pressure
PPG	Photoplethysmography
PTT	Pulse transit time
PWV	Pulse wave velocity
SBP	Systolic blood pressure

CHAPTER I: Literature Review

1.1 HUMAN ARTERIAL STUCTURE AND FUNCTION

1.1.1 General anatomy and physiology

The arterial wall is composed of 3 layers, which are, from superficial to deep, the tunica adventitia, tunica media, and tunica intima (Seeley, Trent, & Tate, 2006). The adventitia contains collagen and some elastin and is attached to surrounding connective tissue (Nichols & O'Rourke, 2005). The tunica media is largely responsible for the mechanical properties of the arterial wall and is composed of elastin, collagen, and smooth muscle. The tunica intima consists of a single layer of endothelial cells, which come into contact with blood as it flows through the vessel, and a thin layer of collagen and elastin. The endothelial cells are responsive to changes in physical and chemical stress and have the capacity to release vasodilators, which in turn act on smooth muscle cells (Nichols & O'Rourke 2005). Although these main features are present in all arteries, the tissue distribution of the arterial wall is not uniform throughout the arterial tree (see Section 1.1.3).

1.1.2 Arterial stiffness

Arterial stiffness refers to the rigidity in the vessel wall (Mackenzie, Wilkinson, & Cockcroft, 2002). Blood vessels must be able to withstand and cushion mechanical stress exerted on their walls from the pressure wave created by ventricular contraction. Furthermore, blood vessels must adapt to the changing metabolic needs of tissues and distribute blood to where it is most needed (Safar & Lacolley, 2007). Arterial compliance is a measure of the ease of distension of an artery in response to changes in

pressure. The major determinants of arterial stiffness include arterial wall composition, smooth muscle tone, and mean arterial pressure (MAP).

1.1.2.1 Tissue composition

Elastin and collagen are the elastic tissues of the artery and smooth muscle is responsible for tension generation in the arterial wall (Nichols & O'Rourke, 2005). The elastic modulus of collagen is much higher than elastin, thus arteries with higher compositions of collagen are stiffer (Nichols & O'Rourke, 2005). Furthermore, arteries with more smooth muscle tissue maintain greater smooth muscle tone and tend to have an increased capacity for increasing arterial stiffness through smooth muscle cell contraction (Seeley et al., 2006).

1.1.2.2 Smooth muscle tone

Increased arterial smooth muscle tone (vasoconstriction) causes increased rigidity in the arterial wall, thus increasing stiffness (Nichols & O'Rourke, 2005). Likewise, decreased arterial smooth muscle tone (vasodilation) reduces tension in the arterial wall causing a decrease in stiffness. Smooth muscle tone is regulated extrinsically by the sympathetic nervous system and locally through endothelial and metabolic derived factors (Wilmore & Costill, 2004). The following details these types of control over smooth muscle tone.

Neurohumoral control. The smooth muscle cells of blood vessels are innervated by sympathetic nerve fibers. At rest, blood vessels are partially constricted through continuous low frequency action potentials from these sympathetic nerve fibers. This low level constriction is referred to as vasomotor tone. Excitation of the vasomotor center in the medulla oblongata causes an increase in smooth muscle cell contraction and reduction in blood vessel lumen diameter proportional to the magnitude of the constriction. Inhibition of the vasomotor center causes reduced smooth muscle cell contraction causing less constriction (or vasodilation) (Wilmore & Costill, 2004). Sympathetic activation also stimulates the release of catecholamines from the adrenal medulla. Blood borne catecholamines bind to alpha-adrenergic receptors on the smooth muscle cells of the arterial wall, which causes vasoconstriction (Seeley et al., 2006).

Local regulation. Changes in the local chemical environment influence blood vessels, which can change in size in response to the metabolic needs of the tissues they supply. Increased metabolism causes a decrease in nutrients (O_2, glucose, amino acids, fatty acids) and an increase in vasodilator substances (CO_2, lactic acid, adenosine, adenosine monophosphate, adenosine diphosphate, acetylcholine , K^+, H^+) with the overall result being vasodilation (Seeley et al., 2006). Furthermore, increased shear stress along the luminal surface of endothelial cells due to increased blood flow stimulates release of endothelial derived relaxing factors (e.g. nitric oxide) which, in turn, act on arterial smooth muscle and cause vasorelaxation (Nichols & O'Rourke, 2005).

1.1.2.3 Mean arterial pressure

The transmural pressure exerted on the arterial wall influences arterial stiffness. As pressure in the artery increases, stress on the arterial wall is transferred from elastin to the less elastic collagen fibers, resulting in an increase in stiffness (Nichols & O'Rourke, 2005).

1.1.3 Central and peripheral artery stiffness

The large arteries closest to the heart (e.g. aorta, common carotid arteries) are elastic arteries, and arterial walls therefore contain higher amounts of elastin compared to collagen. The structure of large elastic arteries allows cushioning of the high pressures created by ventricular contraction (Nichols & O'Rourke, 2005). Moving through the arterial tree from the heart to the periphery, the mean diameter of arteries decreases and they become stiffer and more muscular (e.g. brachial, radial, femoral arteries). In muscular peripheral arteries the amount of elastin is decreased and the content of smooth muscle and collagen is increased in comparison to central elastic arteries (Oliver & Webb, 2003). The function of muscular peripheral arteries shifts from primarily cushioning to regulation of flow distribution, as the relatively larger composition of smooth muscle allows for increased control of blood distribution (Nichols & O'Rourke, 2005).

Systolic blood pressure (SBP) and pulse pressure (PP) are augmented distally through the arterial tree as a result of quicker travelling pulse waves and pulse wave reflections (Laurent et al., 2006). A forward travelling pressure wave, created by

ventricular contraction, travels through the arterial tree and wave reflections are generated at bifurcations and points of high resistance. The reflected wave combines with the forward travelling wave to create the pressure wave. In the elastic central arteries, the reflected waves arrive during diastole and therefore do not result in changes in SBP. However, in the periphery, greater stiffness and closer points of reflected wave creation cause the reflected wave to arrive during systole, which augments SBP and PP (Oliver & Webb, 2003; Safar, 2008) thus contributing to the relative increases in SBP and PP.

1.1.4 Structural and functional alterations in stiffness

Hemodynamic forces (as well as hormones, sodium, and glucose regulation) can cause qualitative and quantitative changes in arterial wall composition and result in increased arterial stiffness (Hayashi, & Naiki, 2009; Zieman, Melenovsky, & Kass, 2005). Some examples of potential changes to the arterial wall include damage to endothelial cells, accumulation of smooth muscle and collagen, and fragmented elastin. These structural and functional alterations thereby cause an increase in arterial wall stiffness and impair the ability of the artery to change size in response to variations in arterial pressure (Zieman et al., 2005).

Increased central elastic artery stiffness reduces the buffering capacity of the aorta and results in increases in SBP and PP. Increased central elastic artery stiffness causes quicker traveling pulse waves and results in pulse wave reflections arriving during systole rather than diastole in central arteries (Figure 1) (Nichols et al., 2008; Oliver & Webb,

2003). Elevated SBP and PP increases left ventricular afterload and has been shown to promote left ventricular hypertrophy in both hypertensive and normotensive individuals (Darne, Girerd, Safar, Cambien, & Guize, 1989; Girerd, Laurent, Pannier, Asmar, & Safar, 1991). With age and cardiovascular disease, stiffness in the central arteries can increase and surpass that of peripheral arteries (Benetos et al., 1993; O'Rourke et al., 2002).

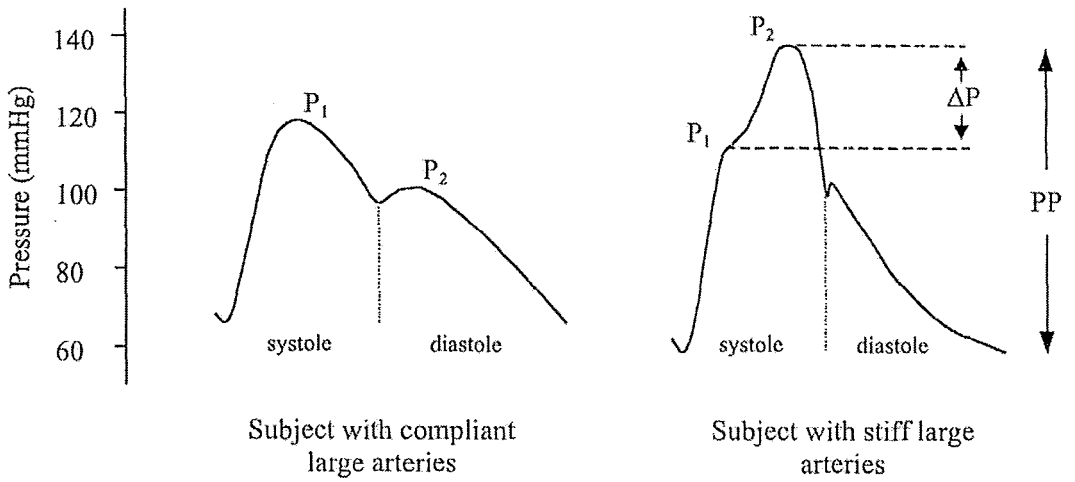

Figure 1. Central artery pressure waveforms in compliant elastic arteries (left) and stiff elastic arteries (right). In healthy, elastic arteries, the forward traveling wave (P_1) determines systolic blood pressure as the reflected wave (P_2) arrives during diastole. In stiff arteries, pulse waves travel faster and the reflected wave arrives during systole, which increases systolic blood pressure (ΔP) and pulse pressure (PP). Modified from Oliver and Webb (2003).

1.1.4.1 Cardiovascular disease

Increased central artery stiffness is a risk marker for cardiovascular diseases such as coronary artery disease, chronic heart failure, and stroke (Laurent et al., 2006) and is associated with multiple cardiovascular disease risk factors such as obesity, smoking,

physical inactivity, hypertension, hypercholestermia, and type 1 and 2 diabetes (Laurent et al., 2006). Furthermore, measures of central artery stiffness are predictors of cardiovascular events and mortality in patients with hypertension, type 2 diabetes, and end stage renal disease (Blacher et al., 1999; Blacher et al., 1998; Boutouyrie et al., 2002; Cruickshank et al., 2002; Laurent et al., 2001; Leone et al., 2008; Safar, 2008) as well as in the general adult and older adult populations (Hansen et al., 2006; Inoue et al., 2009; Meaume et al., 2001; Shokawa et al., 2005). Increased central artery stiffness has been observed in children which cardiovascular disease risk factors such as familial hypercholesterolemia (Aggoun et al., 2000), type 1 diabetes (Hu, Wallensteen, & Gennser, 1996), and obesity (Banach et al., 2009; Tounian et al., 2001; Zebekakis et al., 2005). Peripheral artery stiffness has not been studied as extensively as central artery stiffness; thus the links between peripheral artery stiffness and cardiovascular health have generally not been established. Interestingly, children with obesity have demonstrated reduced stiffness in peripheral arteries, suggestive of vasodilation (Dangardt et al., 2008). The consequences of persistent vasodilation are not known and may, over the long term, lead to alterations in vascular structure and function.

1.1.4.2 Aging and Maturation

Studies consistently demonstrate that central artery stiffness progressively increases with increasing age from childhood independent of an increase in MAP (Avolio et al., 1983; Hansen et al., 1995). Peripheral stiffness has also been shown to increase

from childhood (Avolio et al., 1983; Cheung et al., 2002; Vinet et al., 2005); however, this increase is not as substantial as in the central arteries (Benetos et al., 1993).

Resting and maximal SBP increase in children with age and likely reflect increased body size (Rowland, 1996). In contrast, the effect of maturation on arterial stiffness has not been clearly determined and to our knowledge has only been examined in two studies to date (Ahimastos, Formosa, Dart, & Kingwell, 2003; Lenard et al., 2004). Ahimastos and colleagues (2003) compared central artery stiffness in pre and post pubertal males and females (110 participants). Groups were divided based on age (pre: average 10 y, post: 16 y) and pubertal status was confirmed by salivary hormone levels. Central artery stiffness (measured by pulse wave velocity) was increased in post pubertal males in comparison to pre pubertal males. Females displayed the opposite trend with less central stiffness in the post pubertal group in comparison to pre pubertal. In contrast, Lenard and colleagues (2004) examined central artery stiffness (measured by carotid compliance and distensibility) in early childhood (7-10 y), preadolescence (11-14 y), post adolescence (15-18 y), and young adulthood (15-18 y) (147 participants) and observed increased central artery stiffness from childhood to adulthood with no sex differences. Future study with groups stratified on biological age rather than chronological age are required to discern the relationship between arterial stiffness and maturation.

1.2 MEASURES OF ARTERIAL STIFFNESS

A variety of techniques are commonly used to quantify arterial stiffness non-invasively in human participants. Assessment of pulse wave velocity (stiffness within a

segment of the arterial tree) and arterial compliance and distensibility (stiffness within a small portion of the blood vessel) are the measurement techniques most strongly related with parameters of wall stiffness (Laurent et al., 2006; Nichols & O'Rourke, 2005; Pannier et al., 2002). Arterial stiffness can also be assessed systemically (via flows and pressures in the aorta and carotid) and with pulse wave analysis (e.g. augmentation index).

1.2.1 Compliance and distensibility

Arterial compliance and distensibility are direct measures of arterial stiffness and quantify the absolute and relative cross sectional area change of the artery, respectively, for a given increment in pressure (Figure 2), as described with the following equations:

Equation 1 $$Compliance = \frac{\Delta CSA}{PP}$$

Equation 2 $$Distensibility = \frac{\Delta CSA}{(PP)(CSA_{min})}$$

where ΔCSA is change in cross sectional area, PP is pulse pressure, and ΔCSA_{min} is the minimum cross sectional area. In addition to these parameters, there are also indices which take into account SBP and diastolic blood pressure (DBP) (β-stiffness index) and vessel wall thickness (Young's modulus) (O'Rourke et al., 2002). The carotid artery is a convenient location for measurement of central artery stiffness as the composition of the carotid artery is similar to the aorta and the artery is more accessible for diameter and pressure assessment. Other arteries often used for compliance and distensibility

assessment include the brachial, femoral, and popliteal arteries (Laurent et al., 2006). Stiffer arteries have lower compliance and distensibility and compliant arteries have greater compliance and distensibility.

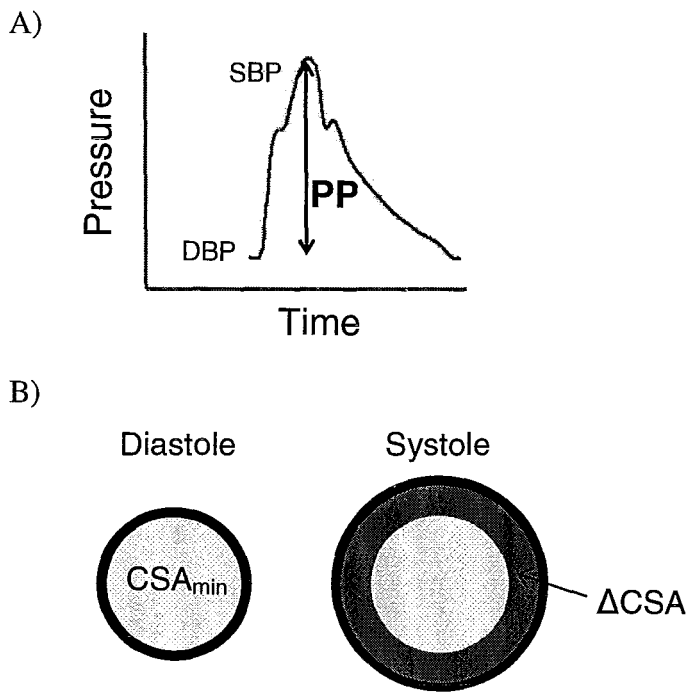

Figure 2. Compliance and distensibility measure the pressure (A) driving the change in cross sectional area (B) of the artery. **A)** Pulse pressure (PP) is the change in pressure from diastole (DBP) to systole (SBP) and causes the change in artery cross sectional area (CSA). **B)** In diastole, the CSA of the artery is smallest (CSA_{min}). The blood pressure increase in systole causes the CSA of the artery to increase (ΔCSA). Arteries that are more compliant (or less stiff) are able to have a greater ΔCSA than more stiff arteries at the same PP. Adapted from Laurent et al. (2006).

Pressures and diameters are ideally obtained simultaneously, throughout the cardiac cycle, and matched beat-to-beat. Blood vessel diameters can be acquired non-

invasively using bi-dimensional ultrasound or magnetic resonance imaging (MRI) (Laurent et al., 2006). For accurate determination of arterial specific compliance it is preferable that pressures are obtained in the vessel of interest because SBP is not uniform in all arteries and is augmented through the arterial tree (O'Rourke et al., 2002) (Section 1.1.3). Carotid (central) blood pressure can be estimated non-invasively by calibrating carotid waveforms to brachial blood pressures (Kelly & Fitchett, 1992; Oliver & Webb, 2003) (Figure 3) or by transfer functions which determine central pressure based on the timing and height of the reflected wave in the radial waveform (Laurent et al., 2006; Swamy et al., 2009).

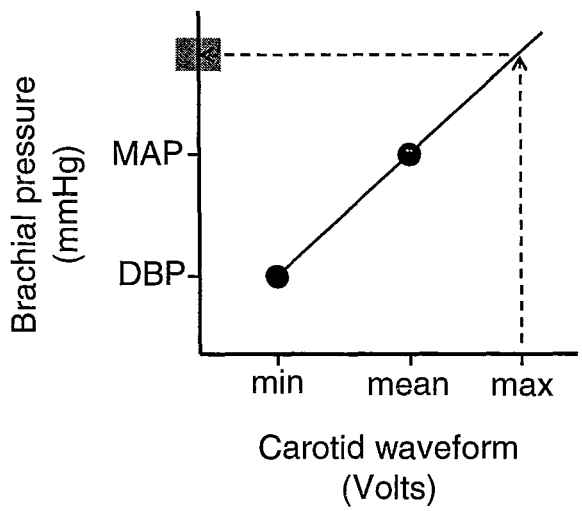

Figure 3. Non-invasive determination of absolute carotid blood pressure. Carotid waveforms, often obtained by tonometry, and brachial blood pressure are acquired simultaneously. With this technique, diastolic blood pressure (DBP) and mean arterial pressure (MAP) are assumed to be the same in all large arteries in the supine position (Nichols & O'Rourke, 2005). The minimum and mean values of the carotid waveform are equated to brachial DBP and MAP, respectively (Kelly & Fitchett, 1992). From this relationship carotid SBP is extrapolated from the maximum of the carotid waveform (illustrated by ■).

An advantage of compliance and distensibility measures is that stiffness is directly determined by relating the change in diameter to the pressure that caused the distension. Furthermore, these direct measures of arterial stiffness are currently the only means to non-invasively investigate the influence of wall thickness (which can be obtained from vessel images) and inward or outward remodeling of the lumen diameter on the elastic properties of the artery (Laurent et al., 2006). Decreased carotid distensibility or compliance is associated with increased risk of cardiovascular disease, cardiovascular disease risk factors, and mortality (Banach et al., 2009; Blacher et al., 1998; Leone et al., 2008; Tounian et al., 2001); however, it has been suggested that compliance and distensibility measures may have less prognostic value than regional measures of stiffness (i.e. pulse wave velocity) for cardiovascular disease (Oliver & Webb, 2003). There are also difficulties associated with obtaining the measurement of pressure in the same site as measurement of vessel diameter and although it is recommended that central blood pressure is estimated, many studies still utilize brachial blood pressures in carotid distensibility assessments (Oliver & Webb, 2003; O'Rourke et al., 2002).

1.2.2 Pulse wave velocity

Pulse wave velocity (PWV) is the speed of travel of the pulse wave through a segment of the arterial tree and increased PWV represents an increase in arterial stiffness. The Moens-Korteweg equation forms the theoretical basis of PWV (Equation 3) (Nichols & O'Rourke, 2005):

Equation 3 $$PWV = \sqrt{\frac{hE}{2R\rho}}$$

where h=artery wall thickness; E=modulus of elasticity; R=artery radius ρ=density of blood. The practical assessment of PWV involves the distance of travel of the pulse wave (or path length) and the pulse transit time (PTT), as shown in Equation 4 (O'Rourke et al., 2002).

Equation 4 $$PWV = \frac{\text{Path length}}{\text{Pulse transit time}}$$

The majority of PWV studies utilize non-invasive methods that involve transducers that are held in place on the skin at pulse points (Laurent et al., 2006). Different waveforms can be used to determine PWV including pressure, distension, volume, and flow (Nichols & O'Rourke, 2005). It is preferable that waveforms are obtained simultaneously rather than sequentially as this reduces errors due to abrupt changes in smooth muscle tone or blood pressure. The arteries of choice for central stiffness are the carotid and femoral. Upper limb PWV is typically determined from the carotid to the radial arteries or brachial to radial arteries. Lower limb PWV is evaluated from the femoral to dorsalis pedis arteries (Laurent et al., 2006).

Methods for analyzing PTT most often involve the time travel of the 'foot' of the wave, located at the end of diastole when the sharp rise in the wave begins, as this is not affected by pulse wave reflections. The foot can be located using a variety of methods including the maximum of the second derivative of the pressure wave (Laurent et al., 2006). Another analysis method locates the foot of the wave based on the high frequency

harmonics (Munakata, Nunokawa, & Yoshinaga, 2003), as these are the main contributors to the sharp inflection in the wave (Nichols & O'Rourke, 2005) (Figure 4).

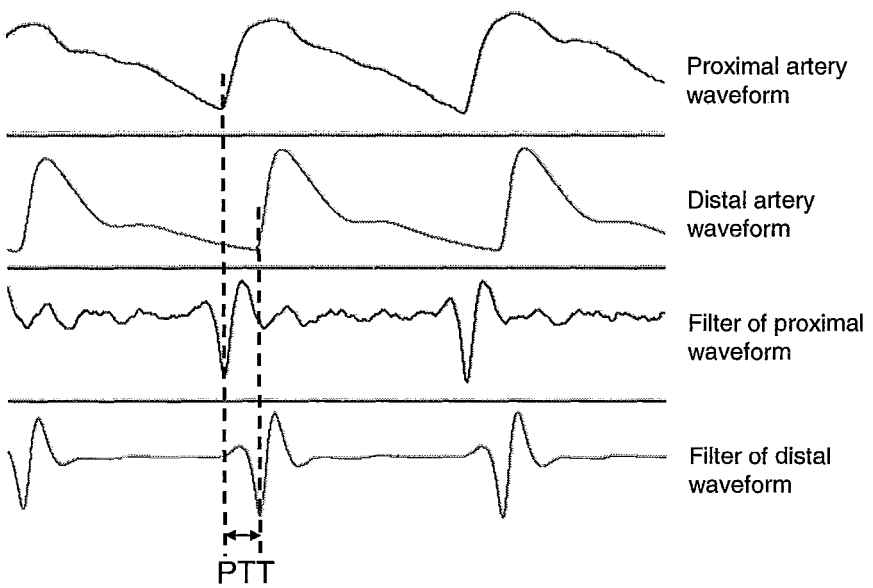

Figure 4. Determination of pulse transit time (PTT) from the high frequencies in the waveforms. The sharp inflection in the wave (i.e. the foot) is largely comprised of high frequency components (Nichols & O'Rourke, 2005). A digital filter can be applied to the waveform to eliminate the low frequencies as well as high frequency noise. A Bandpass filter with a low and high frequency cut off of 5 and 30 Hz, respectively, is recommended. The minimum point of the digitally filtered waveform gives the location of the foot of the wave (Munakata et al., 2003). PTT is calculated as the time difference between the minimum filtered points of the proximal and distal arteries of interest.

PWV is a widely used technique for the assessment of arterial stiffness. It is considered to have high prognostic value (Oliver & Webb, 2003) and changes in PWV are associated with changes in cardiovascular risk, disease, and mortality (Blacher et al.,

1999; Boutouyrie et al., 2002; Cruickshank et al., 2002; Laurent et al., 2001; Meaume et al., 2001). There are limitations and practical problems associated with the non-invasive determination of PWV. Baroreceptor stimulation is a concern when obtaining a carotid signal as this may affect blood pressure regulation (Nichols & O'Rourke, 2005). Also, measures of central PWV from carotid to femoral and upper limb PWV from carotid to radial include more vessels than the vessels of interest. Furthermore, there is no standard for measuring the distance traveled by the pulse wave (path length) (O'Rourke et al., 2002); although, there is evidence that carotid-femoral PWV is most closely matched with intra-arterial aortic PWV when the distance from the sternal notch to the carotid artery is subtracted from the distance from the sternal notch to the femoral artery (Weber et al., 2009). In order to reduce distance measurement errors and the inclusion of vessels other than the aorta, a recent study in our laboratory determined central PWV from the heart (ventricular depolarization) to the femoral artery (Rakobowchuk, Stuckey, Millar, Gurr, & Macdonald, 2009).

1.2.3 Validity and reliability

Non-invasive measures of central PWV and carotid PP have been validated in adult populations against intra-arterial measures (Salvi et al., 2004; Loukogeorgakis et al., 2002; Kelly & Fitchett, 1992). Central, upper limb, and lower limb PWV and carotid compliance and distensibility have been shown to be reliable in adults (Loukogeorgakis et al., 2002; Gamble, Zorn, Sanders, MacMahon, & Sharpe, 1994; Liang et al., 1998).

1.3 CHANGES IN ARTERIAL STIFFNESS WITH AEROBIC EXERCISE

1.3.1 Chronic exercise

Exercise training is used in both the treatment and prevention of cardiovascular disease (Thompson, 2005). Arterial stiffness, which is a marker for cardiovascular disease, is lower in habitually active adults than their inactive peers (Seals et al., 2008; Tanaka et al., 1998) and is inversely related to participant and parent reported physical activity levels in 10 year old children (Schack-Nielsen, Mølgaard, Larsen, Martyn, & Michaelsen, 2005). Adults with impaired vascular structure can improve central (Hayashi et al., 2005; Parnell et al., 2002; Sugawara et al., 2006; Tanaka et al., 2000) and peripheral (Collier et al., 2008; Thijssen, de Groot, Smits, & Hopman, 2007) stiffness with aerobic exercise training.

1.3.2 Acute exercise

The acute changes in arterial stiffness in response to a bout of aerobic exercise have been evaluated following lower limb exercise of different durations and intensities in young healthy adults (Table 1). The majority of these previous studies focused on the acute changes in arterial stiffness in the immediate post exercise period compared to pre exercise as there are technical limitations to assessing arterial stiffness during exercise itself. The acute response to a bout of arm exercise has not been previously characterized.

Table 1. *Changes in central and peripheral (exercised and non-exercised limb) artery stiffness following a bout of aerobic leg exercise.*

Reference	Exercise	Population	Measure	Time points post exercise (min)	Central	Peripheral	
						Exercised	Non-exercised
Kingwell et al., 1997	65% VO_2 peak leg cycling, 30 min	Young sedentary men	c-f PWV f-dp PWV	30, 60	↓ 30	↓ 30	---
Heffernan et al., 2007a	65% VO_2 peak leg cycling, 30 min	Young moderately active men	c-f PWV f-dp PWV	20	↓	↓	---
Heffernan et al., 2007b	Maximal leg cycling	Young resistance trained and sedentary men	c-f PWV f-dp PWV	10, 20, 30	↔	↓	---
Munir et al., 2008	Graded exercise 25-150 W, leg cycling, 12 min	Young healthy men and women	c-f PWV	3, 15, 30, 60	↔	---	---
Lydakis et al., 2008	Dynamic knee extensions, to fatigue	Young healthy men and women	PWA (timing of reflected wave)	During	↑	---	---
Rakobowchuk et al., 2009	Single & multiple Wingate	Young healthy men	h-f PWV f-dp PWV Carotid distensibility	2-60 2, 15, 30, 45, 60	↑ 2-20 ↔	↓ 2-44	---
Naka et al., 2003	Maximal, Bruce protocol, treadmill	Young sedentary men and women	b-r PWV	3-60	---	↓	↑ 2-6 ↓15-60
Sugawara et al., 2003	20-30 Watts, single leg cycling, 5 min	Young healthy men	f-a PWV	2	---	↓	↔
Sugawara et al., 2004	30 Watts, single leg cycling, 5 min	Young healthy men	f-a PWV	2	---	↓	↔
Tordi et al., 2009	Leg cycling, 140 bpm	Young healthy men	c-r PWV	2-30	---	---	↔

PWV pulse wave velocity; *c-f PWV* carotid-femoral PWV; *f-dp PWV* femoral-dorsalis pedis PWV; *f-a PWV* femoral-ankle PWV; *b-r PWV* brachial-radial PWV; *c-r PWV* carotid-radial PWV; *PWA* pulse wave analysis; *h-f PWV* heart-femoral PWV; ↓ significant decrease in stiffness; ↑ significant increase in stiffness; ↔ no significant changes in stiffness, --- no stiffness measure available.

1.3.2.1 Central artery stiffness

The acute changes in central artery stiffness in response to exercise is equivocal (Heffernan et al., 2007a, 2007b; Kingwell et al., 1997; Lydakis et al., 2008; Munir et al., 2008; Rakobowchuk et al., 2009). The apparently conflicting results are likely related to the variations in intensity and duration of exercise as well as the timing of the measures in recovery in various studies. Transient decreases in central artery stiffness have been noted following a prolonged bout of moderate leg cycling 20 (Heffernan et al., 2007a) and 30 (Kingwell et al., 1997) minutes into recovery. This decrease occurred independent of changes in MAP and was hypothesized to be caused by decreased smooth muscle tone from sympathoinhibition or circulating vasodilators (Heffernan et al., 2007a; Kingwell et al., 1997). In contrast, central artery stiffness was increased when measures were obtained during maximal exercise (Lydakis et al., 2008) and immediately following high intensity interval exercise (Rakobowchuk et al., 2009). Possible mechanisms that account for increased central stiffness during and following a bout of exercise include circulating catecholamines (Dimsdale, Hartley, Guiney, Ruskin, & Greenblatt, 1984), increased sympathetic activation (Boutouyrie et al., 1994), and increased MAP (Nichols & O'Rourke, 2005). Other studies have reported no change in central stiffness following exercise (Heffernan et al., 2007b; Munir et al., 2008).

1.3.2.2 Peripheral artery stiffness: Non-exercised limb

Less research is available on the acute changes in peripheral artery stiffness in the non-exercised limb following lower limb exercise. Naka and colleagues (2003)

examined the upper limb peripheral artery stiffness after maximal treadmill exercise and observed an immediate increase in upper limb (non-exercised limb) stiffness following exercise, which they attributed to elevated sympathetic activity and circulating catecholamines. This initial elevation in stiffness was followed by a decrease in stiffness approximately 15 minutes into recovery which was attributed to the influence of circulating vasodilators that originated in the exercised limb dominating the diminishing sympathetic influence (Naka et al., 2003). In contrast, non-exercised limb stiffness has been shown to be unchanged immediately after short duration, low intensity exercise that did not elicit as large a sympathetic or catecholamine response (Sugawara et al., 2004, 2003). Recent findings following moderate intensity exercise also support unchanged peripheral artery stiffness in the non-exercised limb (Tordi et al., 2009).

1.3.2.3 Peripheral artery stiffness: Exercised limb

Most research supports an acute decrease in peripheral artery stiffness following exercise in the exercised limb. These decreases in exercise limb arterial stiffness have been observed following low (Sugawara et al., 2004, 2003), moderate (Heffernan et al., 2007a; Munir et al., 2008; Kingwell et al., 1997), and maximal exercise (Heffernan et al., 2007), and high intensity interval exercise (Rakobowchuk et al., 2009). The decrease in stiffness in the exercised limb appears to occur independently of changes in MAP or blood viscosity suggesting that transient decreases in exercised limb stiffness are a result of reduced vascular tone (Heffernan et al., 2007a; Kingwell et al., 1997; Naka et al., 2003; Sugawara et al., 2003). Metabolites released by the working muscle (e.g. lactate,

adenosine, phosphate, H^+) (Segal, 1994) and vasodilators released by the endothelium associated with increased blood flow to the muscle (nitric oxide, prostaglandin, and endothelium-derived hyperpolarizing factor) (Jungersten, Ambring, Wall, & Wennmalm, 1997) likely cause smooth muscle relaxation in the large conduit arteries of the exercised limb.

1.4 COARCTATION OF THE AORTA

1.4.1 Background

Coarctation of the aorta (CoA) typically accounts for 4-5% of all congenital heart diseases (Hoffman & Kaplan, 2002) and frequently presents with other associated cardiac abnormalities, including ventricular septal defect, aortic or mitral valve abnormalities, and patent ductus arteriosus (Clarkson, Nicholson, Barratt-Boyes, Neutze, & Whitlock, 1983). CoA is often described as a simple narrowing of the descending aorta distal to the origin of the left subclavian artery; however, its presentation is actually often much more complex and the mechanism for development has not been fully elucidated.

There are two main theories for development of the obstruction in CoA: 1) an abnormal extension of ductal smooth muscle tissue into the aorta with an obstruction forming upon closure of the ductus arteriosus following birth, and 2) an abnormal aortic arch development as a result of decreased flows across the fetal aortic arch and isthmus. Regardless of etiology, the narrowing of the root of the descending aorta in CoA causes altered hemodynamics – flow, wall shear stress, and blood pressure – in the aorta and its branches. The arterial vessels proximal to the obstruction (upper limbs, head, and neck)

endure high blood pressure, flows, and shear stress, which are hypothesized to lead to abnormal development and progression of cardiac and vascular tissue. Vessels distal to the stenosis (abdomen and lower limbs) experience relative hypotension, but blood flow is maintained if adequate collateral blood vessels are present (Abbruzzese & Aidala, 2007; Nichols & O'Rourke, 2005). Without repair the majority of CoA patients die before the age of 40 from congestive heart failure, aortic rupture, bacterial endocarditis, or intracranial haemorrhage (Campbell, 1970).

1.4.2 Surgery & intervention

A variety of methods are used to alleviate the pressure gradient (high upper limb/low lower limb) which develops across the aorta in CoA. The common surgical techniques used are: end-to-end anastomosis, subclavian patch repair, patch aortoplasty, tubular bypass grafts, and balloon angioplasty (Gibbs, 2000). The type of repair chosen is dependent on the anatomy of the aortic arch, associated abnormalities, age of the patient, and personal preference of the surgeon (Gibbs, 2000; Toro-Salazar et al., 2002). Infants that are symptomatic (i.e. have significant hypertension or congestive heart failure) commonly undergo immediate intervention. Repair is often delayed in non-symptomatic children until 2-5 years of age when the aorta is larger thereby reducing the likelihood of recoarctation and a subsequent surgical intervention (Gibbs, 2000; Karl, 2007; Rao, 1995).

Prognosis for patients improves considerably following relief of the obstruction; however, even with successful repair, CoA patients have a below normal life expectancy

and higher rates of cardiovascular morbidities such as hypertension and coronary artery disease (Clarkson et al., 1983; Toro-Salazar et al., 2002). Coronary artery disease, sudden cardiac death, heart failure, cerebrovascular accidents, ruptured aortic aneurysm, and death from a subsequent cardiovascular surgery are common causes of late death in individuals with repaired CoA (Cohen, Fuster, Steele, Driscoll, & McGoon, 1989; Toro-Salazar et al., 2002).

1.4.3 Blood pressure

1.4.3.1 Resting hypertension

Most large long-term follow up studies consistently demonstrate that individuals with repaired CoA have a higher than normal prevalence of hypertension (Bobby, Emami, Farmer, & Newman, 1991; Clarkson et al., 1983; Cohen et al., 1989; Hager, Kanz, Kaemmerer, Schreiber, & Hess, 2007; Toro-Salazar et al., 2002). Blood pressure decreases in the days or first few years following surgery (Bouchart et al., 2000; Clarkson et al., 1983), but hypertension is typically observed again approximately 10 years post-surgery in many patients (Clarkson et al., 1983; Toro-Salazar et al., 2002). Hypertension is present in 20-50% of CoA patients 20 to 50 years following surgery (Bobby et al., 1991; Clarkson et al., 1983; Cohen et al., 1989; Hager et al., 2007; Toro-Salazar et al., 2002). The patients included in these large, long-term follow up studies underwent repair between the 1940s (when surgery was first introduced) and 1980s (Bobby et al., 1991; Clarkson et al., 1983; Cohen et al., 1989; Toro-Salazar et al., 2002). During and since this time period technological advances in imaging (MRI, ultrasound) and surgery,

combined with a greater understanding of CoA have improved diagnosis, surgical outcome, and surveillance of those with CoA (Abadir, Sarquella-Brugada, Mivelaz, Dahdah, & Miró, 2009; Karl, 2007; Nichols & O'Rourke, 2005). Thus, the rates of hypertension in patients repaired more recently may not be as high as those previously reported. However, in a more recent cohort (1983-1992), 20% of children repaired in infancy with no residual or recurrent obstruction (as determined by MRI) still had a resting SBP greater than the 95th percentile for their age (O'Sullivan, Derrick, & Darnell, 2002).

The majority of long-term follow up studies measured blood pressure in the brachial artery only and reported this as systemic hypertension. Given that regional differences in blood pressure (i.e. arm and leg) are associated with CoA, this is likely not appropriate. Clinically, a greater than normal difference in SBP in the arm and leg (>15mmHg, referred to as arm-leg SBP gradient) warrants further investigation of recoarctation (Guenthard, Zumsteg, & Wyler, 1996; O'Sullivan et al., 2002; Vriend et al., 2005).

1.4.3.2 Abnormal exercise blood pressure response

Many patients with repaired CoA are normotensive at rest but have an abnormal blood pressure response to exercise. The abnormal blood pressure response to exercise in CoA is described as exercise-induced hypertension and/or a development of an arm-leg SBP gradient (Hager et al., 2007; Vriend et al., 2004). Much of the research on exercise to date has focused on blood pressure response following peak exercise and is often

symptom-limited (Vriend et al., 2004). Nearly one third of individuals with repaired CoA have been found to develop exercise-induced hypertension (when defined as brachial SBP greater than 2 standard deviations from reference load-dependent values) (Hager et al., 2007). Exercise-induced hypertension is common (~20%) even in adults who have normal resting and ambulatory blood pressure (Vriend et al., 2004) and may occur independent of a recoarctation (Guenthard et al., 1996; Hager et al., 2007).

Children and adults with previously repaired CoA that are normotensive at rest and have a normal arm-leg SBP gradient at rest have been found to develop a clinically significant arm-leg SBP gradient (difference in arm and leg SBP greater than 15-20 mmHg) with exercise (Das, Raj, & Shoemaker, 2009; Instebø et al., 2004; Markham et al., 2004). The source of this gradient is not clear and separate arm and leg SBP are often not reported (Das et al., 2009; Markham et al., 2004). Some suggest it is due to marked elevation of arm SBP (Instebø et al., 2004; Markel et al., 1986) while others believe leg SBP does not elevate sufficiently to match the exercise induced elevations in arm SBP (Guenthard et al., 1996).

1.4.3.3 Mechanisms

A number of mechanisms have been proposed to explain hypertension at rest and during and following exercise in individuals with apparently successful CoA repair. The existence of abnormalities in vascular structure and function which are not apparent from image analysis is the prevailing theory and has garnered the most research attention (de Divitiis, Rubba, & Calabrò, 2005). Impaired baroreceptor sensitivity (Beekman, Katz,

Moorehead-Steffens, & Rocchini, 1983; Sehested, Baandrup, & Mikkelsen, 1982) and hyperactivity of the renin-angiotensin system have also been proposed as mechanisms responsible for the altered hemodynamics following repair of CoA.

1.4.4 Abnormalities of vascular structure and function

Vascular abnormalities are present even in patients who have had apparently successful repair of CoA (de Divitiis et al., 2005). The body of literature on vascular structure and function in individuals with CoA is small and the heterogeneity of the population makes interpretation of the findings difficult. The severity of the coarctation, age at time of repair, surgical procedure, the presence of a recoarctation, elevated blood pressure, current age, and other associated cardiac anomalies all likely influence the vascular structure and function in these individuals.

1.4.4.1 Central artery stiffness

Increased aortic stiffness, measured by distensibility and stiffness index, has been noted in the proximal aorta (precoarctation) of children (Ou et al., 2008; di Salvo et al., 2007) and adults (Brili et al., 1998; Vitarelli et al., 2008) with successfully repaired CoA (no evidence of hypertension or recoarctation) in comparison to age matched controls. In contrast, the descending aorta has been shown to have normal distensibility (Brili et al., 1998; Ou et al., 2008; di Salvo et al., 2007; Vitarelli et al., 2008). This stiffening pattern is supported by histological evidence of increased percentage of collagen in the aortic wall proximal but not distal to the coarctation (Sehested et al., 1982).

The relationship between age at time of repair and arterial stiffness is not clear and may be related to the range of ages included in most studies. With a wide range of ages at time repair (2-25 y), Brili and colleagues (1998) found a correlation between age at time of repair and aortic stiffness. Ou and colleagues (2007) did not find a relationship, although their population had a more narrow range of repair (median of 2 months) which may have made it difficult to find a relationship. Thus, the amount of pre-surgical exposure to high pressures and flows proximal to the site of CoA may play a role in elevating stiffness years post repair. It has also been suggested that CoA is a systemic vascular disease of the prestenotic arteries as increased stiffness in the proximal aorta has been noted in infants prior to surgery (Kühn et al., 2009; Vogt et al., 2005) and remains 3 years post surgery (Kühn et al., 2009).

Similar to the findings in the proximal and distal aorta, Brili and colleagues (2005) found increased stiffness (measured via distensibility) in the carotid artery (proximal to the coarctation) and normal stiffness in the femoral artery (distal to the coarctation) in adults approximately 10 years post repair. Of note is that these patients did not have hypertension, recoarctation, or left ventricular hypertrophy; however, they were repaired late (average age of 17 y) which may have influenced the vascular structure and function. Unfortunately, the blood pressures used in most aortic and carotid distensibility analyses were obtained in the periphery: in the arm and in some cases the leg (for descending aortic analysis) (Brili et al., 1998, 2005; Kühn et al., 2009; Ou et al., 2008; di Salvo et al., 2007; Vitarelli et al., 2008; Vogt et al., 2005). This does not follow distensibility recommendations which stress the importance of obtaining diameters and

pressures in the vessel of interest (Laurent et al., 2006; O'Rourke et al., 2002). Therefore, findings on aortic and carotid distensibility should be interpreted with caution.

1.4.4.2 Peripheral artery stiffness

de Divitiis and colleagues (2001) evaluated upper limb (brachial-radial PWV) and lower limb (femoral-dorsalis pedis PWV) stiffness in children and adults (9-60 y) with repaired coarctation. Patients did not have evidence of recoarctation but were not excluded based on hypertension and had significantly higher brachial SBP, DBP, and MAP than controls. In this study individuals with repaired CoA exhibited increased peripheral artery stiffness in the upper limbs following repair compared to controls. This finding of increased arterial stiffness in CoA was limited to the upper limbs as lower limbs had preserved elasticity compared to controls. Increased upper limb stiffness was found to be related to age at time of repair and those repaired before 4 months of age did not have a elevated upper limb arterial stiffness. The authors suggested that the length of exposure to elevated pressures prior to repair is the cause of increased stiffness in the periphery years after repair.

1.4.4.3 Left ventricular hypertrophy and intima media thickness

Given the relationship between arterial stiffness and left ventricle hypertrophy, (Section 1.1.4), it is not surprising that there is a significant correlation between left ventricular mass and arterial stiffness (in the proximal aorta and upper limb) in CoA (Brili et al., 1998; de Divitiis et al., 2003; Ou et al., 2008; di Salvo et al., 2007; Vitarelli

et al., 2008). Furthermore, carotid artery intima media thickness (IMT), a measure of arterial wall thickness and an independent marker of atherosclerosis (de Groot et al., 2004), has been observed to be larger in individuals with repaired CoA (Brili et al., 1998, 2005; Meyer et al., 2005; Vriend et al., 2006) and is associated with late repair and hypertension (Vriend et al., 2006). It is important to note that some studies have found similar left ventricular mass (Kim et al., 2004; Kühn et al., 2009; Swan, Kraidly, Muhll, Collins, & Gatzoulis, 2008) and carotid IMT (Swan et al., 2008) in individuals with CoA and controls.

1.4.4.4 Vascular function

Arterial reactivity to both endothelium dependent (sheer stress) and independent (vasoactive substances) stimuli is impaired in CoA patients after repair (de Divitiis et al., 2001, 2003; Gardiner et al., 1994; Heger et al., 2005; Meyer et al., 2005). This impairment in arterial reactivity is limited to the upper limbs as the lower limbs exhibit normal reactivity when compared to controls (de Divitiis et al., 2001). The relationship between impaired vessel function and age at repair is not clear, with conflicting reports of impairment in function even in patients repaired before 4 months of age (de Divitiis et al., 2001) and no impairment in function in those repaired before 9 years of age (Heger et al., 2005) in comparison to healthy controls.

Forearm blood flow has been found to be higher and vascular resistance lower in normotensive adolescents with repaired CoA (Johnson et al., 2001). This was attributed to a greater baseline vasodilation and increased sympathoinhibitory influence associated

with impaired baroreceptor function. This proposed baseline vasodilation may be complementary to the findings of reduced arterial reactivity to sheer stress and vasoactive substances (de Divitiis et al., 2001, 2003; Gardiner et al., 1994; Heger et al., 2005; Meyer et al., 2005) as the artery may be closer to its maximal dilation at baseline.

1.4.4.5 Aortic arch geometry

Recent investigations by Ou and colleagues (2007, 2008) suggest that arch geometry plays an important role in the development of vascular irregularities associated with CoA. When all arch types are grouped together, individuals with CoA with successful repair have impaired vascular structure and function in comparison to controls; however, subgroup analyses involving arch types reveals that the impairments are limited to those with a triangular aortic arch. Successfully repaired individuals with CoA with a smooth semicircular arch demonstrate similar carotid distensibility, aortic distensibility, aortic PWV, carotid IMT, brachial artery reactivity, and left ventricular mass as controls.

4.3 Exercise

4.3.1 Exercise capacity

Few studies have examined aerobic capacity in individuals with repaired CoA. Significant reductions in peak work load (Hager, Kanz, Kaemmerer, & Hess, 2008), absolute and relative peak oxygen consumption, and peak heart rate (Trojnarska, Gwizdala, et al., 2007) have been noted in maximal symptom-limited exercise tests in comparison to controls or reference values. This decrease in maximal exercise capacity

may be related to altered hemodynamics; however, it is important that the potential for a hypoactive lifestyle (as a result of parental overprotection) is not overlooked (Reybrouck & Mertens, 2005). Other studies have identified that children with repaired CoA have similar maximal work loads (Norozi, Gravenhorst, Hobbiebrunken, & Wessel, 2005) and heart rates (Murphy, Blades, S Daniels, & James, 1989) as reference values and controls, respectively.

Excessive reliance on anaerobic metabolism during exercise has been identified in individuals with repaired CoA and may be caused by reduced blood flow to the limb due to turbulence across the aortic arch (Rhodes et al., 1997; Instebø et al., 2004). Reduced peripheral blood flows with leg exercise, even in the presence of greater femoral vasodilation, have been noted in individuals with repaired CoA (Johnson et al., 1995). These observations may explain the reduced exercise capacity observed during whole body (leg cycling or treadmill running) maximal exercise tests in individuals with repaired CoA. Furthermore, the abnormal flow in the descending aorta may be linked with exercise-induced hypertension (Markel et al., 1986). In this study by Markel and colleagues (1986) children and young adults with CoA (repaired between 1-12 y of age, current age of 8-20 y) performed maximal treadmill exercise and maximal arm ergometry. Repaired children with CoA who developed an arm-leg SBP gradient in response to treadmill exercise had elevated brachial SBP following leg exercise but not arm exercise. The difference in SBP response to arm and leg exercise suggests that abnormal hemodynamics may be responsible for exercise-induced hypertension. With leg exercise, more blood may flow across the site of coarctation to the descending aorta

and working muscles. In the presence of a residual stenosis this may cause turbulent flow and elevate blood pressure. In contrast, with arm cycling less blood flow to the descending aorta may prevent the elevations in blood pressures compared to leg exercise (Markel et al., 1986).

4.3.2 Current recommendations

Individuals with congenital heart disease, such as CoA, are often encouraged to engage in regular physical activity; however, exercise programs are largely based on individual physician judgment (Thaulow & Fredriksen, 2004) and the advice is usually prohibitive rather than prescriptive (Swan & Hillis, 2000). This likely stems from the lack of evidence of beneficial effects of specific exercise training programs and a lack of information on the acute responses to exercise of different modes, intensities, and durations.

1.5 RATIONALE FOR RESEARCH

No study to date has examined the effect of chronic exercise training on vascular function in CoA patients. Furthermore, there is currently a lack of evidence on the effect the residual structural and functional vascular abnormalities present after repair of CoA have on the response to acute exercise in individuals with repaired CoA. Examination of the acute vascular responses to exercise may be useful in the design of exercise training interventions to reduce the progression of secondary cardiovascular disease processes in patients with repaired CoA. Therefore, the purpose of the current study was to determine

whether patients with repaired coarctation of the aorta exhibit impaired arterial stiffness following a moderate bout of each of arm and leg aerobic exercise.

1.6 HYPOTHESES

Continuous moderate intensity arm and leg cycling exercise was performed in children with repaired CoA and age and sex matched controls to test 3 main hypotheses:

1) Individuals with repaired CoA would have greater upper limb and central artery stiffness at rest prior to exercise compared to controls, as has been previously reported.
2) Following exercise, central and non-exercised limb arterial stiffness would increase in both groups due to increased sympathetic activation and blood pressure. Individuals with repaired CoA would have larger increases in central artery stiffness compared to controls due to an elevated blood pressure response.
3) Arterial stiffness would decrease in the exercised limb (arm and leg) in the control group following exercise due to the influence of local metabolic factors and endothelium-released vasodilators. The impaired upper limb vascular function in individuals with repaired CoA would make them less able than the controls to respond to arm exercise with a local decreases in upper limb arterial stiffness, but they would have normal responses in the lower limb following leg exercise.

CHAPTER II: Methods

2.1 PARTICIPANTS

Nine children with coarctation of the aorta (7 males, age: 12 ± 3 y) and 9 healthy age and sex matched controls (7 males, age: 11 ± 3 y) completed the study (Table 2). CoA participants were recruited from a local pediatric cardiology unit (McMaster University Medical Centre, Hamilton, ON, Canada). All CoA participants underwent routine clinical screening, which included patient history, echocardiograms, and electrocardiographs, prior to being invited to participate in the study to determine if they met inclusion and exclusion criteria. Patients who underwent a second surgical intervention, had a residual gradient (determined by arm-leg SBP gradient >15 mmHg and systolic peak flows >3m/s in the descending aorta with evidence of diastolic runoff), hypertension (defined as SBP or DBP > 95th percentile for age), and left ventricular hypertrophy (septal and posterior wall dimensions > 2 z-scores for body surface area) were excluded from the study. Patients with Shone syndrome, subaortic ridge, renal problems, and/or other major associated heart deficiencies, were also excluded.

Table 2. *Participant characteristics*

	CoA	Control	p-value
Age, y	12 ± 3	11 ± 3	0.72
Age at time of repair, y	2 ± 3	---	---
Range	Newborn to 9 y		
Interval from repair to study, y	9 ± 3	---	---
Range	5 to 15		
Height, m	1.50 ± 0.14	1.50 ± 0.22	0.94
Weight, kg	49.2 ± 10.2	41.9 ± 18.2	0.31
BMI, kg/m^2	21.8 ± 3.9	17.8 ± 3.3	0.03
BMI percentile	72 ± 31	52 ± 25	0.15

Data are mean ± SD. *n*=9 per group. *BMI* body mass index.

Patients underwent repair for the coarctation at median age of 2 years (range: newborn to 9 y) and the median time from repair to the testing session was 8 y (range 5 to 15 y). Repair methods used to alleviate the flow gradient across the aortic arch were: end-to-end anastomosis (n=5), subclavian flap (n=1), balloon dilation (n=2), and simultaneous repair of coarctation and patent ductus arteriosus by ligation (n=1). In addition to the coarctation, participants had been diagnosed with ventricular septal defect (repaired, n=1), patent ductus arteriosus (repaired, n=1), and bicuspid aortic valve (n=4). Two of the participants with bicuspid aortic valve also had mitral valve dysplasia (n=1) and trivial aortic insufficiency (n=1). One participant had a minor flow acceleration across the isthmus. Echocardiograms were performed on the control subjects, recruited from the local community, using the same clinical protocol as the CoA patients to ensure there were no undiagnosed heart abnormalities. No participant recruited as a healthy control was excluded due to an abnormal echocardiogram.

All procedures were reviewed and approved by the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board, conforming to the Helsinki Declaration on the use of human subjects. Prior to participation written, informed consent was obtained from the parent/guardian and assent from the child.

2.2 STUDY DESIGN

This study employed a cross-sectional design. All participants completed bouts of arm and leg exercise in a randomized order on separate occasions. Measures of arterial stiffness and blood pressure were taken before and after exercise on each testing session.

2.3 EXPERIMENTAL PROTOCOL

Participants arrived at the laboratory at the same time of day for both testing sessions. Measurements were all conducted 2-3 hours postprandial and participants were instructed to abstain from caffeine on the day of testing to control for the vascular changes that occur with nutritional status and caffeine consumption. All measurements were conducted with the participant in the supine position in a temperature controlled room (22-24°C).

Resting baseline (PRE) measures of central and peripheral artery stiffness were obtained following 15 minutes of supine rest and arm and leg blood pressures were taken simultaneously immediately before the start of exercise after approximately 25 minutes of supine rest. Participants then completed a 20 minute bout of either arm (881, Monark Exercise AB, Vansbro, Sweden) or leg (818E, Monark Exercise AB, Vansbro, Sweden) cycling in the upright seated position at a workload which elicited a heart rate 50% above resting heart rate. Participants cycled at a cadence of 50-60 revolutions per minute, while heart rate was continuously monitored and the workload was adjusted to achieve the target heart rate. Following exercise participants returned immediately to the supine position. Arm and leg blood pressure was obtained immediately after exercise (within 1-2 minutes) and stiffness measures were obtained at 5 minutes (POST 5) and 15 minutes (POST 15) post exercise.

Due to limited participant availability, one CoA patient and their age and sex matched control performed the leg and arm exercise interventions on the same day. For these two participants, the exercise sessions were separated by a rest period of 15 minutes

following POST 15 measures and heart rate was monitored to ensure it had returned to pre exercise levels. Furthermore, two participants from each group were unable to complete the test at the same time of day. These participants were excluded from day-to-day variability analyses.

2.3.1 Heart rate and blood pressure

Single-lead electrocardiography (ECG) was used to monitor heart rate at rest and during exercise and for arterial stiffness analyses. Arm and leg blood pressures were evaluated simultaneously using two automated oscillometric blood pressure devices (Arm: model CBM-7000, Colin Medical Instruments, San Antonio, TX; Leg: Dinamap Pro 100, Critikon LLC, Tampa, Flordia, USA). Arm blood pressure was assessed in the brachial artery using appropriately sized cuffs placed around the upper arm and leg blood pressure was evaluated in the popliteal artery with the cuff placed around the thigh. Due to a large upper leg circumference, the cuff was placed distal to the knee on one CoA participant. Three blood pressure measures were taken PRE and the values obtained on the final two were averaged, as the first blood pressure measurement with automated devices has been shown to overestimate blood pressure (Carter, Ray, Downs, & Cooke, 2003). A singular blood pressure measure was taken immediately post exercise (within 1-2 minutes). MAP and PP were calculated by the following equations:

Equation 5 $$MAP = \frac{2}{3} DBP + \frac{1}{3} SBP$$

Equation 6 $$PP = SBP - DBP$$

2.3.2 Arterial Stiffness

Two methods were used to assess arterial stiffness: PWV, an indirect, whole limb measure; and arterial distensibility, a direct, artery specific measure.

2.3.2.1 Arterial Distensibility

Carotid distensibility was measured in the right common carotid artery, a representative central artery, using ultrasound imaging and photoplethysmography (PPG) (Rakobowchuk et al., 2008). Two digital video clips of the carotid artery were acquired at each time point using B-mode ultrasound at a rate of 10 frames per second for 10 consecutive heart cycles (System FiVe, GE Medial Systems, Horten, Norway). A 10-MHz linear array probe was positioned parallel to the long axis of the right common carotid artery and landmarks were used to ensure similar probe placement on multiple images and across testing sessions. Carotid artery pressure waveforms were obtained simultaneously in the right carotid artery, distal to ultrasound probe, using a non-invasive PPG probe (Model No. MLT1020PPG, ADInstruments, Colorado Springs, CO, USA). PPG probes have an infrared emitting diode and a phototransistor detector. Blood volume, a strong absorber of infrared radiation, increases as the artery dilates which causes a change in the amplitude of the detected signal (Loukogeorgakis et al., 2002).

In order to determine absolute carotid blood pressure, the carotid waveforms were calibrated to brachial blood pressure, which was simultaneously obtained with a tonometer-cuff system (Model CBM-7000, Colin Medical Instruments, San Antonio, TX, USA). The system uses radial waveforms, acquired with an applanation tonometer at the

wrist, and cuff-acquired absolute brachial blood pressures to calculate continuous brachial blood pressure. The continuous brachial blood pressure was used to calibrate the carotid waveforms. Briefly, the calibration is based on the assumption that DBP and MAP are the same in conduit arteries in the supine position (Nichols & O'Rourke, 2005). Therefore, the minimum and mean carotid values were equated to brachial DBP and MAP. Carotid SBP was extrapolated from this linear relationship based on the maximum value of the carotid waveform (Kelly & Fitchett, 1992). The calibration was done each beat to obtain beat-to-beat carotid blood pressures which were matched to the corresponding vessel diameters (Rakobowchuk et al., 2008).

Arterial wall images were stored in DICOM format and analyzed offline by the same investigator using a semi-automated edge detection system (AMS II, Chalmers University of Technology, Göteborg, Sweden) which facilitates the assessment of arterial diameter and wall IMT. Briefly, a region of interest was selected in the artery and landmarks were used to facilitate a similar selection area between images for the same participant. Lumen diameter was determined from the proximal interface of the adventitia on the near wall to the proximal aspect of the intima on the far wall based on changes in gradient and intensity pixel to pixel. The video clip with the best image quality and carotid waveforms was analyzed at each time point. The minimum and maximum diameters and pressures were used to calculate distensibility using the following equation (O'Rourke et al., 2002):

Equation 7 $$Distensibility = \frac{\Pi\left(\frac{d_{max}}{2}\right)^2 - \left(\frac{d_{min}}{2}\right)^2}{(PP)\left(\frac{d_{min}}{2}\right)^2}$$

where d_{max} is the maximum carotid lumen diameter during the heart cycle, d_{min} is the minimal carotid lumen diameter, and PP is carotid pulse pressure.

2.3.2.2 Pulse wave velocity

PWV was measured centrally and peripherally using a combination of ECG, PPG, and applanation tonometry and was obtained simultaneous to the arterial distensibility measures described in the previous section. PPG probes were placed on the surface of the skin over the right carotid, femoral, and dorsalis pedis arteries (Model No. MLT1020PPG, ADInstruments, Colorado Springs, CO, USA). Radial pressure waveforms were obtained with an applanation tonometer at the wrist (Model CBM-7000, Colin Medical Instruments, San Antonio, TX, USA). The radial applanation tonometer has an internal time delay of 16 ms (unpublished observations) which was taken into account in analyses.

Pressure waveforms were acquired simultaneously in all vessels for at least consecutive 30 beats at 1000 Hz using a data acquisition hardware system (Powerlab model ML870, ADInstruments, Colorado Springs, CO, USA), and recorded by software (Chart v6.1.2, ADInstruments, Colorado Springs, CO, USA). PWV was calculated with the time (PTT) and distance (path length) travelled by the pulse wave, using the following equation (Davies & Struthers, 2003):

Equation 4 $PWV = \frac{\text{Path length}}{\text{Pulse transit time}}$

PTT was determined by the time travel of the 'foot' of the wave. The foot of the wave was located at the end of diastole when the sharp inflection in the wave began and is largely composed to high frequency harmonics (Nichols & O'Rourke, 2005). Therefore, a digital filter was applied to the pulse wave to eliminate the low frequencies as well as high frequency noise. A bandpass filter with a low and high frequency cut off of 5 and 30 Hz, respectively, was used. The foot of the wave was located as the minimum point of the digitally filtered wave form (Munakata et al., 2003). To calculate PTT, the time from the arrival of the foot of the wave at the proximal point was subtracted from the time of the arrival of the foot of the wave at the distal location (Laurent et al., 2006). PTT was determined for 30 consecutive beats and the data was visually inspected and irregular values were removed. The remaining PTT values were averaged to obtain a single value at each measurement time point. The distance travelled by the pulse wave (path length), was determined by measuring between sites with anthropometric tape.

PWV was calculated centrally, in the upper limb, and in the lower limb as summarized in Table 3. Central PWV was calculated as the time delay between ventricular depolarization (R-spike on ECG signal) to the arrival of the pulse wave at the femoral artery. The path length was measured as the distance from the sternal notch to the femoral probe. Upper limb PWV was determined from the time delay between the arrival of the pulse wave at the carotid and radial arteries and the path length was calculated as the sternal notch to the site of the radial probe minus sternal notch to the site

Table 3. *Segmented pulse wave velocity assessments*

Pulse wave velocity	Pulse transit time	Path length
Central	Ventricular depolarization to femoral artery	Sternal notch to femoral probe
Upper limb	Carotid artery to radial artery	Sternal notch to radial probe minus sternal notch to carotid probe
Lower limb	Femoral artery to dorsalis pedis artery	Femoral probe to dorsalis pedis probe

of the carotid probe. Lower limb PWV was calculated from the PTT and distance between the femoral and dorsalis pedis arteries. We were unable to obtain a signal in the femoral artery in one CoA participant; subsequently this participant was excluded from PWV analysis.

2.3.3 Intima-media thickness

Carotid IMT was analyzed using the same arterial video clips and software as the arterial diameters (used in distensibility analysis). Far-wall IMT was determined from the proximal aspect of the intima to the proximal interface of the adventitia at end diastole. A total of 10 IMT measures were averaged per participant.

2.4 STATISTICAL ANALYSIS

Statistically the data was was analyzed using a two-factor (group x time) analysis of variance (ANOVA) with repeated measures, with a Tukey post hoc procedure to evaluate specific differences between means (Sigma Stat 3.1, Systat, San Jose, CA,

USA). An alpha level of 0.05 was considerd statistically significant. Normal Gaussian distributions of the data were assessed using Kolmogorov-Smirnov tests and natural logarithmic transformations were performed as required. Participant characteristics and baseline variables were analyzed using independent (between groups) and dependent (within groups) t-tests, where appropriate, and the Mann-Whitney Rank Sum test was used in the case of non-normal distributions. Data are pressented as Means ± SD, unless otherwise noted.

CHAPTER III: Results

3.1 BASELINE VARIABLES

There were no differences at resting prior to exercise (baseline) within each group between days for any of the variables measured ($p>0.05$), thus, all baseline data is presented as the mean of the both testing days (Table 4).

Table 4. *Baseline variables*

Variables	CoA	Control	p-value
Heart Rate, bpm	75 ± 17	72 ± 7	0.60
Brachial			
SBP, mmHg	110 ± 7	105 ± 7	0.15
DBP, mmHg	54 ± 7	53 ± 5	0.82
MAP, mmHg	72 ± 7	70 ± 4	0.46
PP, mmHg	56 ± 3	52 ± 7	0.12
Popliteal			
SBP, mmHg	114 ± 9	113 ± 8	0.72
DBP, mmHg	52 ± 3	51 ± 4	0.39
MAP, mmHg	73 ± 5	72 ± 4	0.53
PP, mmHg	62 ± 7	62 ± 5	0.96
Arm-Leg SBP Gradient, mmHg	-5 ± 9	-8 ± 7	0.39
Carotid			
PP, mmHg	36 ± 6	31 ± 5	0.05
LD Min, mm	6.1 ± 0.5	5.4 ± 0.3	<0.01
LD Max, mm	7.0 ± 0.6	6.1 ± 0.3	<0.01
LD Mean, mm	6.5 ± 0.6	5.8 ± 0.3	<0.01
IMT, mm	0.44 ± 0.06	0.42 ± 0.03	0.53
Distensibility, $mmHg^{-1}$	0.0093 ±0.0022	0.0102 ± 0.0042	0.59
PWV			
Central, m/s	2.7 ± 0.3	2.5 ± 0.4	0.33
Upper Limb, m/s	6.1 ± 0.5	6.8 ± 0.9	0.08
Lower Limb, m/s	7.3 ± 1.7	6.7 ± 0.9	0.43

Data are mean ± SD. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *PP* Pulse pressure, *LD* lumen diameter, *IMT* intima media thickness, *PWV* pulse wave velocity.

3.1.1 Heart rate and blood pressure

Baseline heart rate, brachial SBP, DBP, and MAP were not different between participants with repaired CoA and controls. There were also no differences in popliteal SBP, DBP, MAP or the arm-leg SBP gradient between the two groups (Table 4).

3.1.2 Carotid artery measures

Carotid artery PP was higher in the repaired CoA group in comparison to the controls. The participants with repaired CoA also had significantly larger minimum, maximum and mean lumen carotid artery diameters. Carotid artery IMT and distensibility were not different between the two groups (Table 4).

3.1.3 Pulse wave velocity

Central PWV was not different between the repaired CoA and control groups, nor was lower limb PWV. There was a trend in the upper limb for slower PWV in the repaired CoA versus controls ($p=0.08$). Within group analyses showed similar PWV in the upper and lower limbs in the controls (6.8 ± 0.9 versus 6.7 ± 0.9 m/s, $p=0.78$), and a trend for lower PWV in the upper limbs in comparison to the lower limbs in the participants with repaired CoA (6.1 ± 0.5 versus 7.3 ± 1.7 m/s $p=0.09$) (Table 4).

3.1.4 Body mass index

Body mass index (BMI) was significantly higher in the repaired CoA group than control group (Table 2, $p<0.05$). For this reason, we compared healthy weight (BMI

percentile 5 to 85; n=4) and at risk of over weight and overweight (BMI percentile > 85; n=5) (Kuczmarski & Flegal, 2000) CoA participants for variables which were different between the groups in the main analysis presented above. There were no differences between the two subgroups in upper limb PWV (6.1 ± 0.6 versus 6.1 ± 0.5 m/s, p=0.82), carotid artery mean lumen diameter (6.5 ± 0.5 versus 6.6 ± 0.7 mm, p=0.85), or carotid PP (35 ± 8 versus 37 ± 5 mmHg, p=0.61).

3.1.6 Reproducibility of the measurements

The reproducibility of the measurements in the study was determined by the baseline measurements prior to exercise on the two days. The coefficient of variations for carotid distensibility, PP, lumen diameter, and IMT were 10, 9, 2, and 4%, respectively. The coefficient of variations for central, upper limb, and lower limb PWV were 4, 5, and 11%, respectively. These coefficients of variation are comparable to those previously reported by our laboratory in adult populations (Rakobowchuk et al., 2008, 2009) and by others (Liang et al., 1998; Loukogeorgakis et al., 2002).

3.2 ACUTE RESPONSE TO ARM AND LEG CYCLING

3.2.1 Heart Rate

The average heart rate during leg cycling was not different between participants with repaired CoA and the controls (114 ± 19 versus 115 ± 15 bpm, p=0.95). Although the workload was adjusted throughout the arm and leg exercise tests to maintain heart rate at the target level, there were variations in heart rate throughout. The peak heart rate

recorded during leg cycling was also not different between the two groups (136 ± 23 (CoA) versus 135 ± 14 bpm (controls), p=0.92). The average and peak heart rate attained during arm cycling was comparable between groups (average: 115 ± 19 (CoA) versus 111 ± 9 bpm (controls), p=0.58; Peak: 137 ± 21 (CoA) versus 132 ± 12 bpm (controls), p=0.56).

3.2.2 Blood pressure

3.2.2.1 Leg exercise

Brachial SBP (Figure 5A) and popliteal SBP (Figure 5B) were significantly elevated immediately following leg exercise ($p<0.01$ for both, main effects for time). There were no differences between the groups for brachial or popliteal SBP at any time point (p=0.14 and p=0.54, respectively). Brachial SBP increased more in the repaired CoA group than controls but was not significant (p=0.12). The arm-leg SBP gradient was not altered with leg cycling exercise (CoA: PRE: -3 ± 10 mmHg, POST: -2 ± 13 mmHg; Control: PRE: -6 ± 9 mmHg, POST: -7 ± 5 mmHg; p=0.83) and was not different between the groups (p=0.37). Brachial MAP did not significantly change with leg cycling in either group (CoA: PRE: 77 ± 9, POST 5: 75 ± 9, POST 15: 74 ± 8; Control: PRE: 72 ± 5, POST 5: 70 ± 10, POST 15: 70 ± 9; p=0.10) and was not different between the groups (p=0.22).

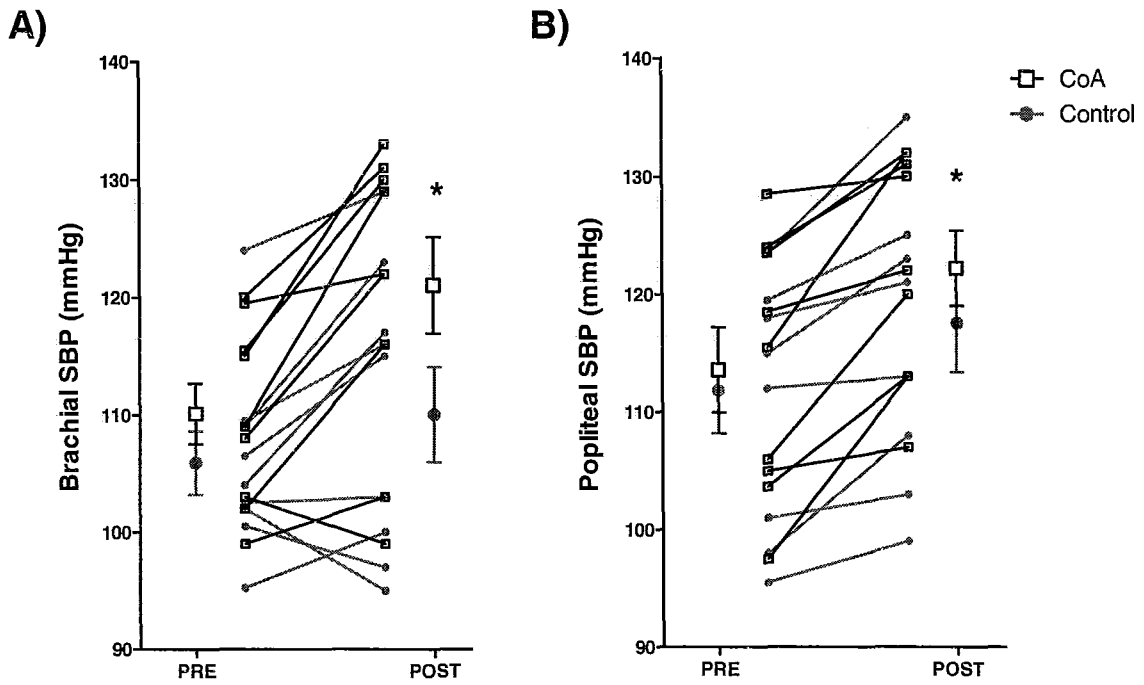

Figure 5. Systolic blood pressure (SBP) response to leg cycling. A) Brachial artery SBP and B) popliteal artery SBP before (PRE) and immediately after (POST) leg exercise. Values are means ± SEM; n=9 per group. *indicates $p<0.05$ vs. PRE; main effect for time.

3.2.2.1 Arm exercise

Brachial artery SBP was significantly elevated immediately after arm cycling in repaired CoA and control groups ($p<0.01$; Figure 6A). Popliteal artery SBP was also significantly elevated following arm cycling in both groups ($p<0.01$; Figure 6B). There were no differences between the two groups in brachial or popliteal SBP ($p=0.16$ and $p=0.87$, respectively). The arm-leg SBP gradient was -6 ± 11 mmHg before and -1 ± 18 mmHg after arm cycling in the repaired CoA group and -10 ± 6 mmHg before and -8 ± 8 mmHg after in the control group with no differences within groups over time ($p=0.38$) or

between groups (p=0.19). There were also no significant changes in brachial MAP following arm exercise (CoA: PRE: 76 ± 7, POST 5: 74 ± 7, POST 15: 74 ± 8; Control: PRE: 71 ± 6, POST 5: 72 ± 7, POST 15: 71 ± 7; p=0.21) and was not different between the groups (p=0.28).

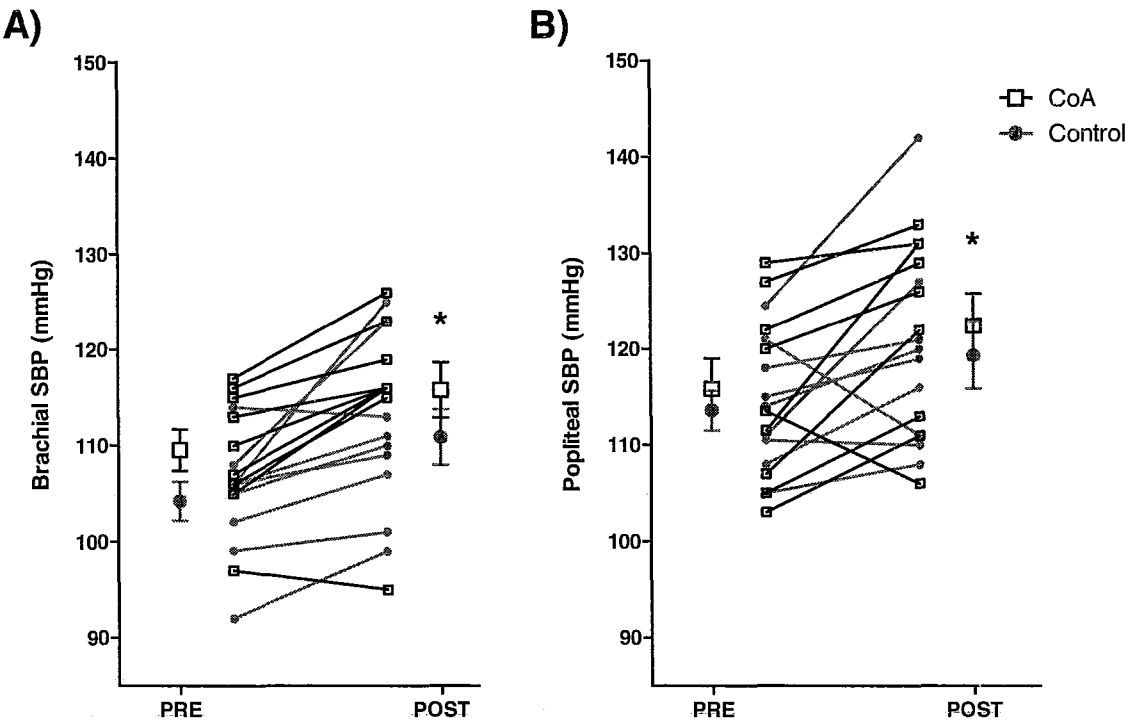

Figure 6. Systolic blood pressure (SBP) response to arm cycling. A) Brachial artery SBP and B) popliteal artery SBP before (PRE) and immediately after (POST) arm cycling. Values are means ± SEM; n=9 per group. *indicates p<0.05 vs. PRE; main effect for time.

3.2.4 Central artery stiffness

3.2.4.1 Carotid artery distensibility

Carotid distensibility did not change following leg cycling (p=0.12) and there was no difference between the repaired CoA and control groups (p=0.79; Figure 7A) at any time point. Carotid distensibility was not different from baseline at either 5 or 15 minutes following arm cycling (p=0.18) and there were no differences between the groups (p=0.81; Figure 7B)

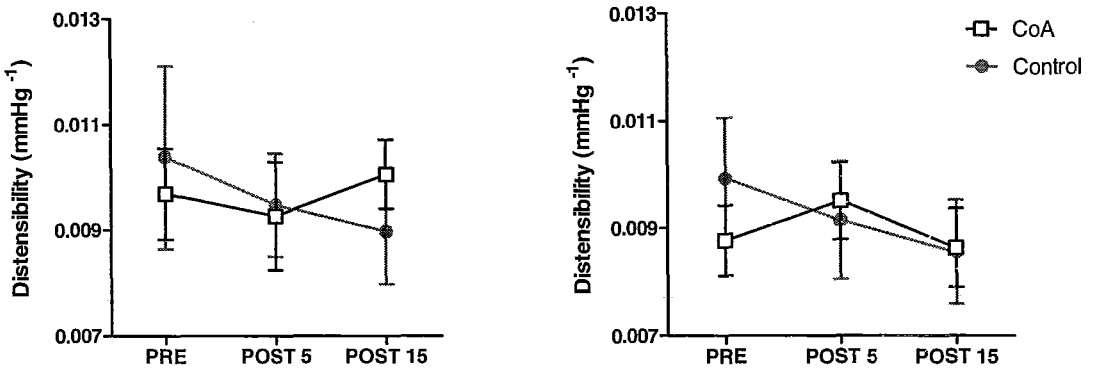

Figure 7. Carotid distensibility before (PRE) and after (5 and 15 minutes) A) leg cycling and B) arm cycling. Values are means ± SEM; *n*=9 per group.

3.2.4.2 Central pulse wave velocity

Central PWV was reduced from baseline at the 5 and 15 minute time points following leg cycling in the repaired CoA group and did not change in the control group (p<0.05, group by time interaction; Figure 8A). Central PWV was increased 5 minutes

following arm cycling and returned to baseline 15 minutes post exercise ($p<0.01$, main effect for time) but no differences were observed between groups ($p=0.16$; Figure 8B).

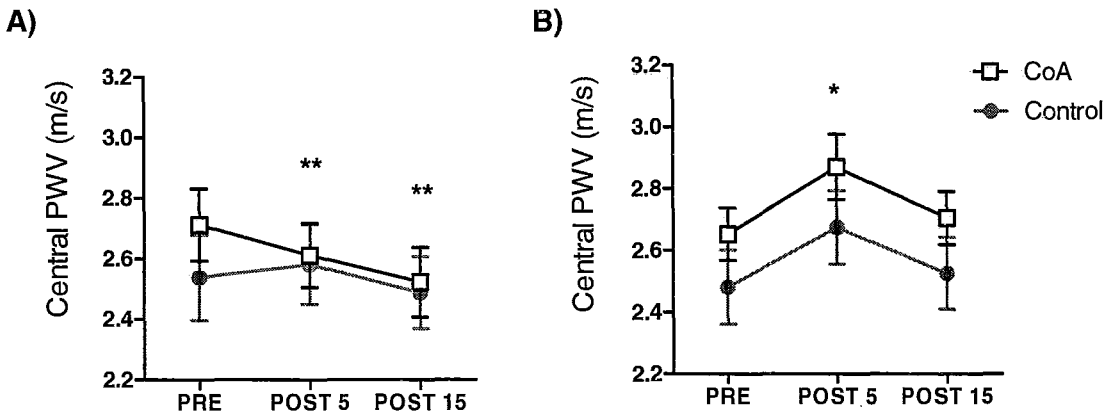

Figure 8. Central pulse wave velocity (PWV) before (PRE) and 5 and 15 minutes after (POST 5 and 15) A) leg cycling and B) arm cycling. Values are means ± SEM; *n=8* per group. * indicates $p<0.05$ vs. PRE; main effect for time. ** indicates $p<0.05$ versus PRE within CoA; group x time interaction.

3.2.4 Non-exercised limb arterial stiffness

Upper limb PWV did not significantly change over time in either group following leg exercise ($p=0.81$), however, the repaired CoA group had slower upper limb PWV than controls at all time points ($p<0.05$, main effect for group, Figure 9A). There were no significant changes in lower limb PWV following arm exercise (Figure 9B) with time ($p=0.21$) or between groups ($p=0.70$).

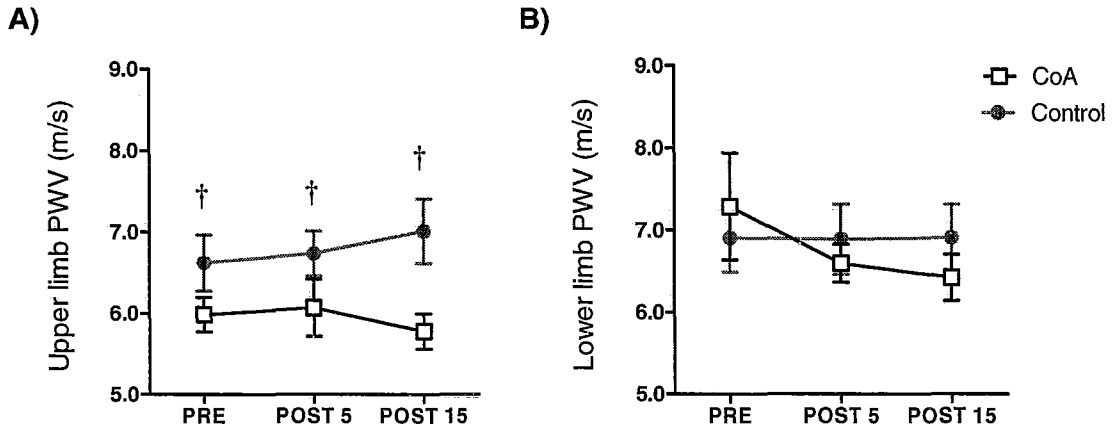

Figure 9. Non-exercised-limb pulse wave velocity (PWV). A) Upper limb PWV before (PRE) and 5 and 15 minutes after (POST 5 and 15) leg cycling. B) Lower limb PWV before and after arm cycling. Values are means ± SEM; *n=8* per group. † indicates $p<0.05$ versus Control; main effect for group.

3.2.5 Exercised limb arterial stiffness

Lower limb PWV (Figure 10A) did not significantly change following leg cycling exercise with time (p=0.85) or between groups (p=0.24). Upper limb PWV (Figure 10B) was reduced 5 minutes after arm cycling and returned to baseline by 15 minutes post exercise ($p<0.05$, main effect for time). There was also a main effect for group in the upper limb with lower PWV observed in the upper limb of individuals with repaired CoA than in the controls at all time points ($p<0.05$).

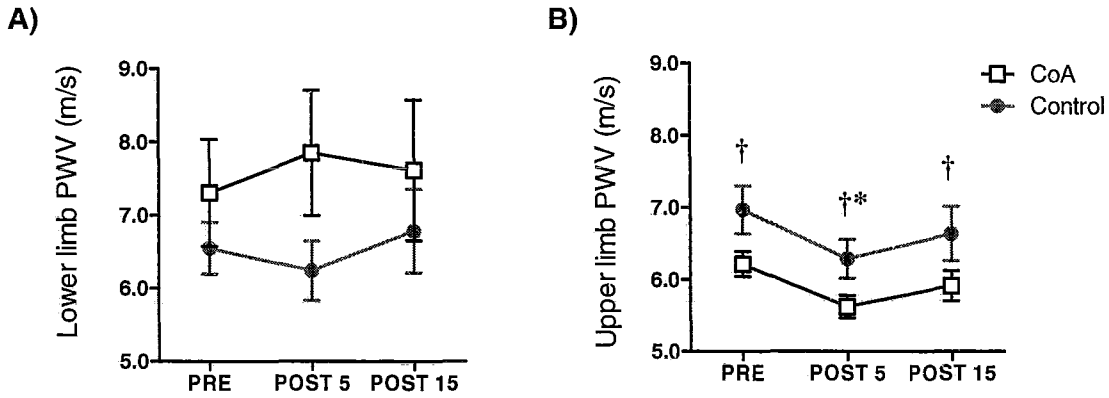

Figure 10. Exercised-limb pulse wave velocity (PWV). A) Lower limb PWV before (PRE) and 5 and 15 minutes after (POST 5 and 15) leg cycling. B) Upper limb PWV before and after arm cycling. Values are means ± SEM; *n=8* per group. * indicates $p<0.05$ vs. PRE; main effect for time. † indicates $p<0.05$ versus Control; main effect for group.

CHAPTER IV: Discussion

Even with successful repair, concerns remain about altered vascular structure and function and the higher than normal prevalence of hypertension and coronary artery disease in individuals with CoA. The current study demonstrates that arterial stiffness is not inevitable in children with successfully repaired CoA and the vascular response to submaximal exercise is not impaired.

4.1 CENTRAL ARTERIES

Previous investigations report greater stiffness in the carotid artery (Brili et al., 2005) and proximal aorta (Brili et al., 1998; Kühn et al., 2009; Ou et al., 2008; di Salvo et al., 2007; Vitarelli et al., 2008; Vogt et al., 2005) of children and adults with repaired CoA. In contrast, our findings demonstrate that despite a period of pre-operative exposure to high pressures and flows, greater central artery stiffness (i.e. carotid distensibility and central PWV) is not present 5-15 years post repair. Ou and colleagues (2007, 2008) have found normal carotid artery and proximal aortic stiffness in individuals with repaired CoA with normal aortic arch geometry. The individuals with a triangular arch, however, had many vascular irregularities including greater central stiffness and left ventricular mass (Ou et al., 2007, 2008). Although the current study did not evaluate arch geometry, the findings by Ou and colleagues highlight that not all individuals with repaired CoA have greater arterial stiffness, and pre-operative exposure to high pressures and flows alone may not cause arterial stiffness years post repair. In fact, even a very mild residual stenosis has been found to be a strong predictor of elevated SBP and increased carotid IMT (Vriend et al., 2005). It is likely that the level of arterial stiffness

in individuals with repaired CoA is an interaction between pre-surgical exposure to high pressures and flows as well as post-surgical structural abnormalities (Ou et al., 2007).

The differing findings of normal central stiffness in children with repaired CoA in the current study may be related to participant characteristics. Some previous studies had differences in SBP and DBP in repaired CoA, in comparison to the controls (Brili et al., 1998, 2005; Kühn et al., 2009; Vogt et al., 2005) and were conducted in adults several years post surgery (Brili et al., 1998, 2005; Vitarelli et al., 2008). Also, by not including individuals with left ventricular hypertrophy we may have excluded those with elevated stiffness, as stiffness causes left ventricular hypertrophy (Darne et al., 1989; Girerd et al., 1991) and these are correlated in individuals with repaired CoA (Brili et al., 1998). Furthermore, our stiffness assessment at the carotid artery may not be reflective of the proximal aorta, which is most frequently assessed in CoA research. It is also important to note that previous investigations of distensibility did not measure pressures and diameters in the same vessel (Brili et al., 1998, 2005; Kühn et al., 2009; Ou et al., 2008, 2007, 2008; di Salvo et al., 2007; Vitarelli et al., 2008; Vogt et al., 2005), thus the results may not be an accurate estimation of stiffness.

Further evidence that the repaired CoA participants in the current study did not have as impaired vascular structure as those studied previously (Brili et al., 1998, 2005; Meyer et al., 2005; Vriend et al., 2006) is demonstrated by the similar carotid IMT in both groups. Carotid PP, however, was significantly elevated in the children with repaired CoA. PP is used as a rudimentary index of arterial stiffness (Oliver & Webb,

2003); thus, this may be an early indicator of vascular stiffening in the children with repaired CoA.

To our knowledge, this is the first study to report carotid artery diameters in individuals with repaired individuals with CoA. We found that children with successfully repaired CoA have larger carotid artery lumen diameters. This study was not designed to delineate mechanisms; thus, these can only be inferred. Larger lumen diameters may be caused by outward remodeling in response to pre-surgical elevations in flows. Outward remodeling is believed to occur to compensate for increased flows in attempt to restore normal shear stress and wall tension (Ward, Pasterkamp, Yeung, & Borst, 2000). It is well established that lumen diameters increase with aging (Nichols & O'Rourke, 2005) and atherosclerosis (Kiechl & Willeit, 1999) and lumen diameter size has been proposed as an early indicator of cardiovascular disease (K. Jensen-Urstad, M. Jensen-Urstad, & Johansson, 1999; Mannami, Baba, & Ogata, 2000). Larger lumen diameters have been noted in individuals with cardiovascular disease risk factors, such as elevated blood pressure and obesity, independent of plaque formation (K. Jensen-Urstad et al., 1999; Mannami et al., 2000; Ozdemir, Artaş, Serhatlioğlu, & Oğur, 2006). Without carotid flows (and given that carotid PP was higher in CoA), we cannot rule out that lumen diameter enlargement may have occurred in the years since repair. Further, it is possible that larger lumen diameters are a result of a decreased vascular tone, caused by impairment in vasoregulation (K. Jensen-Urstad et al., 1999), although this is less likely in light of normal carotid distensibility. Due to the reported relationship between lumen diameter size and obesity (K. Jensen-Urstad et al., 1999; Ozdemir et al., 2006), the higher

BMI in the children with CoA must be taken into consideration when interpreting the findings. However, further sub analysis of our data indicate that there was no difference in lumen diameters of overweight and normal weight children with repaired CoA, which suggests that the larger lumen diameters are not a result of differences in BMI. Further study will be required to determine if the enlarged lumen diameter in children with repaired CoA observed in this study indicates the onset of other vascular alterations in individuals with repaired CoA.

4.2 PERIPHERAL ARTERIES

As expected, lower limb artery stiffness was not different in the current study between CoA and controls, in agreement with previous findings (de Divitiis et al., 2001). In the upper limb there was a trend for reduced upper limb artery stiffness in the individuals with CoA which became significant with the exercise. This decreased upper limb artery stiffness compared to controls is contrary to what we hypothesized and to what has been previously reported with the PWV technique (de Divitiis et al., 2001, 2003) but is supported by other findings (Johnson et al., 2001). de Divitiis and colleagues (2001, 2003) found significantly greater brachial-radial PWV in individuals with repaired CoA and the contrasting findings of the current study may be a result of different study population characteristics. The CoA group in the previous study included hypertensives and those who had significantly higher brachial SBP, DBP, and MAP than the control group. Moreover, the participants were 9-60 years old and current age was

not taken into consideration; therefore, we do not know if the children in the study had increased upper limb arterial stiffness.

Our study population is more closely matched with Johnson and colleagues (2001) and our findings are complementary. Johnson and colleagues (2001) studied adolescents with CoA approximately 13 years post repair. The individuals with CoA and age-matched controls had similar SBP, DBP, and MAP. Forearm blood flow was increased and forearm vascular resistance was decreased in the individuals with repaired CoA, which is suggestive of reduced vasomotor tone and may explain our findings of decreased arterial stiffness in the upper limb. Reduced vasomotor tone was attributed to sympathoinhibition caused by impaired baroreceptor function (Johnson et al., 2001).

Reduced artery stiffness in the upper limb has also been noted in obese children and adolescents (Dangardt et al., 2008). Although the children with CoA in the current study had a significantly higher BMI than the controls, sub-group analysis of healthy weight and overweight/at risk of overweight CoA noted similar artery stiffness in both groups. Thus, differences in BMI between the CoA and controls are therefore likely not the cause of the observed between group differences in upper limb artery stiffness.

The implications of reduced vasomotor tone and whether it may lead to alterations in future vascular structure and function in individuals with repaired CoA remains to be explored. Furthermore, it is possible that, similar to the carotid artery, lumen diameters in the conduit arteries of the upper limb are larger in the children with repaired CoA than controls as a result of outward remodeling. The Moens-Korteweg equation theoretically relates lumen diameter inversely to PWV (Nichols & O'Rourke, 2005). The effect of

lumen diameter on PWV is thought to be minimal but has not been explored. Increased lumen diameter could potentially cause reduced PWV and incorrectly infer that wall stiffness is reduced. Larger lumen diameters along with reduced PWV in the upper limb have been reported in obese children (Dangardt et al., 2008). Therefore, the decrease in stiffness may be methodological and not physiological; however, future study will be required to assess the effect of lumen diameter on PWV.

4.3 ACUTE RESPONSE TO ARM AND LEG CYCLING EXERCISE

This is the first study to report the acute responses of arterial stiffness in individuals with repaired CoA following exercise. The findings from the current study suggest that children with successful repaired CoA have a similar stiffness response to moderate intensity submaximal arm and leg exercise as age and sex matched controls.

4.3.1 Blood pressure

An abnormal blood pressure response to exercise is used clinically to indicate the existence of a residual coarctation or of recoarctation in individuals with previously repaired CoA (Das et al., 2009; Guenthard et al., 1996; Markham et al., 2004; Vriend et al., 2004). In the current study, the lack of drastic differences in brachial SBP both between the groups and within the CoA group following exercise compared to rest suggests that the children in the current study with CoA were successfully repaired. Despite this lack of a statistically significant blood pressure response to exercise, there were non-significant differences in the blood pressure response in children with repaired

CoA in comparison to controls. Following leg exercise, brachial SBP tended to increase more in the children with repaired CoA than the controls. This trend for group differences was not observed following arm exercise. These leg exercise specific findings are consistent with previous reports which suggest that abnormal flows across the site of coarctation with leg exercise may cause reduced flows in the descending aorta and therefore be linked to elevated post exercise blood pressure in the upper limbs (Markel et al., 1986). With arm exercise, the lower demand for blood flow in the lower limb may cause less turbulent blood flow across the site of coarctation and mitigate abnormal elevations in SBP in the upper limb that are seen with leg exercise (Markel et al., 1986). Thus, arm exercise may offer the potential for an exercise stimulus which does not stimulate abnormal elevations in SBP.

4.3.2 Central artery stiffness

In the current study, central artery stiffness, as measured with the PWV technique, decreased following leg exercise in participants with CoA and did not change with exercise in the control participants. Our hypothesis was that central artery stiffness would be increased in both groups following both arm and leg exercise due to elevations in sympathethic mediated contraction of vascular smooth muscle and activation of vascoconstriction through myogenic mechanisms. Interestingly, the blood pressure responses to arm and leg exercise indicate that there was a trend for elevated blood pressure following leg but not arm exercise so we would actually predict central artery stiffness to increase as a result. We are unsure of how to interpret our current findings in

light of previous literature and the proposed mechanisms, but suggest that residual alterations in the structural and functional properties of the central arteries, and in particular the descending aorta, in individuals with repaired CoA may make the extrapolation of previous literature inaccurate and unfounded.

In agreement with our hypothesis, central artery stiffness, measured with the PWV technique, increased following arm exercise in both groups. Transient increases in central artery stiffness have been demonstrated in healthy individuals during maximal exercise (Lydakis et al., 2008) and following high intensity sprint interval exercise (Rakobowchuk et al., 2009). With moderate intensity exercise no change (Munir et al., 2008) or decreased (Kingwell et al. 1997; Heffernan et al. 2007a) central artery stiffness has been noted. Decreased central artery stiffness following exercise in these previous studies (Kingwell et al. 1997; Heffernan et al. 2007a) was hypothesized to result from decreased smooth muscle tone from sympathoinhibition or circulating vasodilators. The finding of increased central artery stiffness following arm cycling in the present study is different than the response we observed following leg cycling and those previously reported with a similar intensity (Heffernan et al., 2007a; Kingwell et al., 1997) and may be attributed to the greater sympathetic activation associated with arm compared to leg exercise (Fadel et al., 2001). The increase in central artery stiffness appears to reflect increased vascular tone of the arterial wall as MAP did not significantly change at any post exercise time point compared to the resting baseline in either group. Potential mechanisms for the increase in vascular tone include increased sympathetic activation (Boutouyrie et al., 1994) and/or circulating catecholamines (Dimsdale et al., 1984). Of

clinical significance is the observation that we found no between group differences in central artery PWV following arm exercise indicating that children with previous CoA and controls had similar stiffness in their central arteries following moderate intensity arm exercise. We hypothesized that children with CoA would have a higher MAP following exercise and that this would in turn cause a greater increase in stiffness; however, the current exercise challenge did not result in the expected group specific blood pressure increases.

Despite changes in central PWV with arm cycling, carotid artery distensibility, as measured directly with the combined ultrasound and tonometry technique, was unchanged with both arm and leg exercise. These technique specific differences in measures of central stiffness may suggest that the PWV technique is more sensitive to acute changes in arterial stiffness with exercise than artery specific measurements of distensibility. Even following a high intensity sprint interval exercise challenge, we have not detected significant changes in central artery stiffness measured directly with ultrasound and tonometry while changes in central PWV were detected (Rakobowchuk et al., 2009). We hypothesize that because the assessment of central PWV incorporates the contributions of the aorta from the level of the aortic valve to the femoral artery, while the distensibility measures only reflect the changes at one site in the carotid artery, the central PWV changes are more reflective of the complete section of the arterial tree which is responsible for the majority of the elastic energy buffering of the central arteries.

4.3.3 Non-exercised limb arterial stiffness

In the current study there were no changes in non-exercised limb arterial stiffness following either moderate arm or leg exercise. Maximal exercise has been shown to acutely increase non-exercised limb artery stiffness, likely through an increase in vasoconstriction caused by increased sympathetic activity and circulating catecholamines (Naka et al., 2003). In contrast to this previous study of maximal exercise responses, no change in non-exercised limb artery stiffness has been reported following low and moderate intensity leg cycling (Sugawara et al., 2003, 2004; Tordi et al., 2009). Thus, it appears that a submaximal exercise stimulus may not result in a large enough sympathetic influence to alter artery stiffness in the non-exercised limb.

4.3.4 Exercised limb arterial stiffness

The low to moderate intensity of exercise in the current study may also explain the lack of decrease in lower limb arterial stiffness following leg exercise in comparison to previous studies which used moderate and high intensity exercise (Heffernan et al., 2007a, 2007b; Kingwell et al., 1997; Rakobowchuk et al., 2009). However, Sugawara and colleagues did note decreased exercised limb stiffness following low intensity leg cycling (Sugawara et al., 2003, 2004). In this study of young healthy men they acquired PWV within two minutes post exercise in comparison to the five minute post exercise time point used in the present study. Given the moderate intensity and relatively short duration (20 minutes) of exercise in the current study it is possible that by 5 minutes post

exercise endothelial and muscle-derived vasodilators had washed from the exercising limb vessel bed, thus accounting for the lack of changes in exercised limb artery stiffness.

In agreement with previous research (Heffernan et al., 2007a, 2007b; Kingwell et al., 1997; Naka et al., 2003; Rakobowchuk et al., 2009; Sugawara et al., 2004, 2003), we observed a transient decrease in artery stiffness in the exercised limb following arm cycling. This decrease in artery stiffness likely reflects relaxation in the arterial wall caused by metabolites released by the working muscle (e.g. lactate, adenosine, phosphate, H^+) (Segal, 1994) and vasodilators released by the endothelium associated with increased blood flow to the muscle (nitric oxide, prostaglandin, and endothelium-derived hyperpolarizing factor) (Jungersten et al., 1997; Kingwell et al., 1997; Naka et al., 2003; Rakobowchuk et al., 2009; Sugawara et al., 2003). The divergent findings related to exercised limb arterial stiffness in the arm and the leg may reflect the smaller muscle mass of the arms and differences in metabolism (i.e. greater lactate in exercising arm in comparison to leg) (Freyschuss & Strandell, 1967; Ahlborg & M. Jensen-Urstad, 1991) which may contribute to increased vasodilation of the upper limb with exercise. These acute decreases in exercised limb artery stiffness following exercise may be linked to the observation of decreased resting artery stiffness in the exercised limb that is found with training (Naka et al., 2003). Therefore, given the acute reduction in artery stiffness following a bout of arm exercise, exercise training with arm cycling may offer a stimulus to improve vascular stiffness in the upper limb. This might be of particular importance to individuals with repaired CoA due to previous reports of increased upper limb artery stiffness in this population.

We expected that children with repaired CoA would be less able to respond to arm exercise with a local decreases in artery stiffness. We hypothesized that exercise would produce less local vasodilation because arterial reactivity to both endothelium dependent (sheer stress) and independent (vasoactive substances) stimuli has been shown to be impaired in the upper limb of individuals with repaired CoA (de Divitiis et al., 2001, 2003; Gardiner et al., 1994; Heger et al., 2005; Meyer et al., 2005). In contrast to these previous reports, in the current study we did not observe elevated upper limb arterial stiffness in the CoA group. We also did not observe any differences in the vascular responses in the exercised limb to arm cycling between children with repaired CoA and controls. This may be explained by 1) the children with repaired CoA did not have impaired vascular function and/or 2) the exercise stimulus was not great enough toreveal differences in vascular function.

The children in the current study were repaired before 9 years of age and arterial reactivity has been shown to be preserved in children repaired before this age (Heger et al., 2005). However, this finding is not consistent and de Diviitis and colleagues (2001) showed impairment of arterial reactivity even in children repaired before 4 months. Thus, we are not able to conclude that the relatively early age of repair in this study preserved vascular function of the upper limbs and resulted in a similar stiffness response as the controls. Lifestyle factors (e.g. physical activity) have the potential to improve vascular function (Clarkson et al., 1999) and must not be overlooked. Parent-reported physical and sedentary activity in the current study suggests that the repaired CoA and control groups had similar levels of activity, which may have influenced the similar

stiffness response. Previous reports have indicated an increased potential for a hypoactive lifestyle in individuals with repaired congenital heart disease (Reybrouck & Mertens, 2005). It is possible that elevated levels of inactivity influences the impairment of vascular function observed in previous investigations of individuals with repaired CoA.

The stimulus used to assess arterial reactivity is designed to produce maximal sheer stress on the vessel wall. With a low sheer stress stimulus (i.e. low to moderate intensity exercise), vascular responses to exercise may appear to be the same in individuals with repaired CoA as healthy controls. Moreover, the abnormal blood pressure response often observed in children with repaired CoA is in response to maximal exercise (Hager et al., 2007; Vriend et al., 2004). The resting baseline differences we observed in children with repaired CoA and controls (increased carotid lumen diameter and decreased upper limb PWV) potentially related to outward remodeling or reduced resting vasomotor tone and therefore may affect the response to exercise at higher intensities. Therefore, high intensity or maximal exercise may be required to determine if this group of repaired children with CoA exhibits an impaired stiffness response to exercise (Figure 11).

4.4 LIMITATIONS

The current study is limited by a small sample size; however, it is comparable to others in the literature examining the acute response to exercise in healthy individuals (Heffernan et al. 2007a; Rakobowchuk et al. 2009; Sugawara et al., 2003; Kingwell et al.

1997) and to various stimuli (e.g. exercise, low body negative pressure) in individuals with repaired CoA (Chen et al., 2008; Das et al., 2009; Gardiner et al., 1994; Gidding, Rocchini, Moorehead, Schork, & Rosenthal, 1985; Johnson et al., 1995, 2001; Markel et al., 1986; Sehested et al., 1982). A larger study sample may have been achieved if we

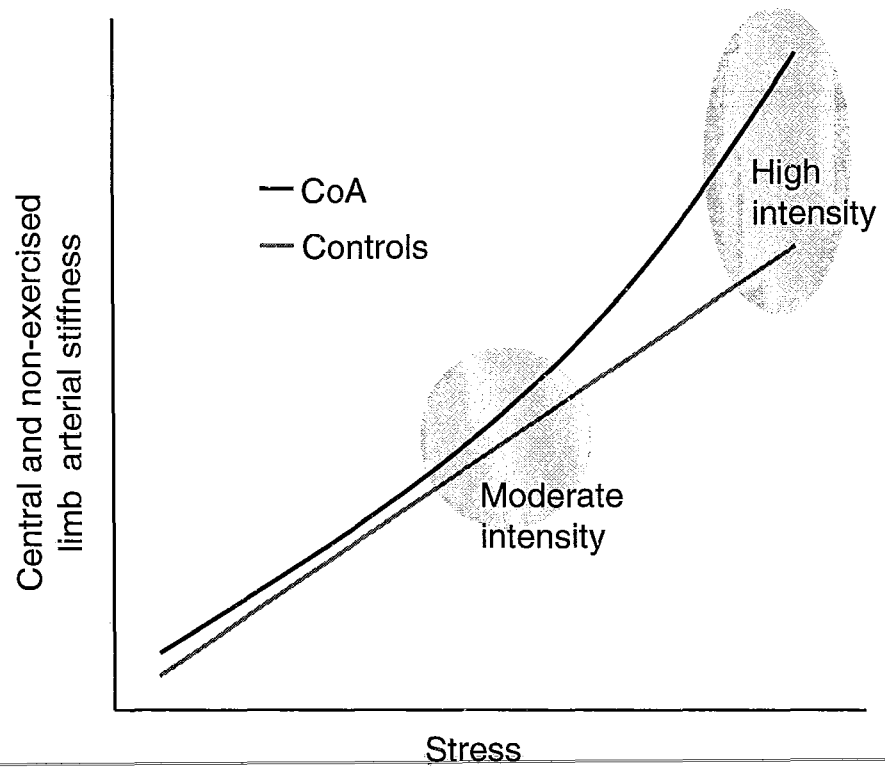

Figure 11. Schematic for the potential of a greater stimulus to reveal differences in vascular stiffness in individuals with repaired CoA. The current study reflects moderate intensity exercise and as exercise intensity increases we may observe differences in vascular function.

included older participants and individuals with hypertension, as is frequently done in large studies in this area (de Divitiis et al. 2001; Guenthard et al. 1996; Trojnarska et al. 2007; Vriend et al. 2005; Heger et al. 2005; Ou et al. 2008). Given that our primary

outcome variable, arterial stiffness, is directly influenced by age and blood pressure we believe more homogeneity in the CoA group was achieved by the small sample size. Nonetheless, differences between groups, especially in the blood pressure response to exercise, may have been apparent with more participants. We also acknowledge that the selection criteria may have caused our study sample to not be reflective of the population as a whole. However, we believe this study represents a subset of children with CoA with successful repairs and favorable outcomes. Furthermore, this study would have benefited from biological matching (e.g. peak height velocity) of controls with children with CoA rather than relying on chronological age. However, the literature on maturation and arterial stiffness is sparse and equivocal (Ahimastos, Formosa, Dart, & Kingwell, 2003; Lenard et al., 2004) and our participants were matched similarly to others in the cardiovascular literature (de Divitiis et al., 2001; Markel et al., 1986; Murphy et al., 1989; Ou et al., 2008). Regardless, we acknowledge that an assessment of biological maturation would have been advantageous.

There were also limitations in the methodologies employed. The assessment of upper limb PWV from the carotid to radial arteries includes vessels not in the upper limb, however this method is frequently employed (Dangardt et al., 2008; Tordi et al., 2009). Alternatively, brachial to radial PWV (de Divitiis et al., 2001; Naka et al., 2003) could have been assessed, although the short distance makes this measure more prone to error and less reliable. Upper limb PWV from using the subclavian to radial segment may have been the most appropriate, however, technical limitations made this difficult. In addition, technical limitation and measurement artifacts make assessments of arterial

stiffness and blood pressure difficult during exercise. Instead, we relied on post exercise measures to determine if the exercise resulted in differences between the groups. Therefore, we cannot rule out that the response during the exercise bouts in the two groups was different and that the arterial stiffness assessment 5 minutes post exercise may have been too late to detect these changes. Furthermore, the intensity of the exercise may not have been great enough to reveal group differences, thus, higher intensity exercise may have been more appropriate.

4.5 FUTURE DIRECTIONS

In light of the heterogeneity of the population of individuals with CoA (e.g. age at time of repair, type of surgery, severity of the coarctation) and the varying and conflicting findings in the population, longitudinal study may be required to delineate the changes and time course of the vascular abnormalities that present in this population. At the very least, an extensive cross-sectional examination is warranted. Follow up investigations in our study sample will be required to determine if the baseline differences in carotid lumen diameter and upper limb PWV are early indicators of cardiovascular disease processes.

Future research should evaluate activity levels and intensity (via accelerometry) as exercise is known to influence vascular structure and function. Lower limb exercise intolerance in this population (unpublished observations) may influence the intensity of exercise performed in daily life and in part explain the vascular impairments. Additional studies of the acute and chronic responses to exercise of different modes and intensities

will be required to support our conclusions that arm exercise may be an appropriate and beneficial exercise stimulus (acutely and chronically) in this population. Measurement of blood flows in the exercised and non-exercised limb and across the aorta may be useful when addressing this issue. Examination of a full range of exercise intensities should also be performed as this may reveal acute differences that were indiscernible in the current study. Furthermore, exercise training may have the potential to improve cardiovascular health and prognosis the most in individuals with a less successful outcome, thus, these individuals should be included in future research.

4.6 CONCLUSIONS

Our study demonstrates that children with successfully repaired CoA may not be predisposed to greater arterial stiffness in the large conduit arteries proximal to the coarctation. However, the carotid and upper limb arteries may have enlarged lumen diameters or reduced vasomotor tone, which may reflect early signs of cardiovascular disease processes. The response to exercise suggests that children with successfully repaired CoA do not have impaired stiffness following an acute bout of moderate arm and leg exercise. However, differences may become apparent with higher intensity exercise. Finally, the acute reductions in upper limb arterial stiffness following arm exercise and normal elevations in blood pressure suggest that moderate intensity aerobic arm exercise training may be a safe and effective way to improve vascular structure and function in children with repaired CoA.

S.1 SUPPLEMENTARY DATA

Parent-reported physical activity

Arterial stiffness is lower in habitually active adults than inactive adults (Seals et al., 2008; Tanaka et al., 1998). Child-reported physical activity (with help of the parent) has been shown to be inversely related to arterial stiffness in boys and girls (age 10) (Schack-Nielsen et al., 2005). Since it is known that physical activity influences arterial stiffness, we examined parent-reported physical and sedentary activities in children with repaired CoA and age and sex matched controls.

Parents completed a activity questionnaire related to frequency and duration of typical sedentary activity (computer, television, videogames, telephone) and physical activity (mild, moderate, vigorgous) of their child. Sedentary activity was assessed by duration and physical activity was given a weighted score based on duration and intensity (Appendix A). There were no differences between parent-reported physical activity scores (CoA: 13 ± 5, Control: 12 ± 4; p=0.48) or sedentary activity scores (CoA: 6±2, Control: 5±1; p=0.15) in the children with repaired CoA and the controls.

The findings show that the typical physical and sedentary activities (as reported by their parents) of the participants with repaired CoA and the controls were similar. This suggests that differences noted between groups may not be related to physical activity levels. Perhaps more intriguing, the few significant differences between the children with repaired CoA and controls may be reflective of similar physical activity levels. Future research should evaluate activity levels with accelerometry to get a more

accurate picture of physical activity and intensity and how these influence arterial structure and function in children with repaired CoA.

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Appendices

Appendix A: Parent-reported activity questionnaire

ACTIVITY QUESTIONNAIRE

Dear Parent:
The purpose of the following questionnaire is to help us evaluate the activity habits of your child. Please be as accurate as possible in your answers. Feel free to add any details that seem relevant.

1. How would you compare the physical activity of your child to that of her/his friends?
   - ☐ My child is as active as her/his friends
   - ☐ My child is more active than her/his friends
   - ☐ My child is less active than her/his friends
   - ☐ Not sure

2. How would you compare the activity of your child with that of her/his sibling(s)?
   - ☐ My child is as active as her/his sibling(s)
   - ☐ My child is more active than her/his sibling(s)
   - ☐ My child is less active than her/his sibling(s)
   - ☐ Not applicable (no siblings)
   - ☐ Not sure

3. How many hours in a typical day is your child engaged in the following activities:

Activity	Less than 1 hour	1-2 hours	2-3 hours	3-4 hours	4-5 hours	More than 5 hours
TV						
Video games						
Computer						
Phone						

4. How many hours in a typical day is your child engaged in light, moderate, and vigorous physical activity (See examples below):

Physical Activity	Less than 30 minutes	30 mins. - 1 hour	1-2 hours	More than 2 hours
Light				
Moderate				
Vigorous				

Light Physical Activity
Light walking
Stretching

Moderate Physical Activity
Brisk walking
Skating
Bike riding
Swimming
Playing outdoors
Dancing

Vigorous Physical Activity
Running
Soccer
Supervised weight training
Basketball
Aerobics
Fast dancing
Fast swimming

5. Which mode of transportation does your child use to travel to and from school?
   - ☐ Car / bus
   - ☐ Walking
   - ☐ Biking
   - ☐ Other:_____

   If biking or walking; what is the total time spent actively travelling per day?
   - ☐ 0-10 minutes
   - ☐ 10-20 minutes
   - ☐ 20-30 minutes
   - ☐ More than 30 minutes

6. In your opinion, is your child as active as she/he should be?
   - ☐ Yes
   - ☐ My child is too active
   - ☐ My child is not sufficiently active
   - ☐ Not sure how much physical activity she/he needs

7. If your child is not as active as she/he should be, what, in your opinion, is the reason? (you can select more than one answer)
   - ☐ Lack of interest
   - ☐ Disease
   - ☐ Lack of suitable conditions
   - ☐ Other: _____
   - ☐ I don't know

Weighted scores for parent-reported activity questionnaire

Question 3: Sedentary activities

	Time (hours)					
	<1	**1-2**	**2-3**	**3-4**	**4-5**	**>5**
TV	1	2	3	4	5	6
Video games	1	2	3	4	5	6
Computer	1	2	3	4	5	6
Phone	1	2	3	4	5	6

Question 4: Physical activities

	Time (hours)			
	<0.5	**0.5-1**	**1-2**	**>2**
Light	1	2	3	4
Moderate	2	4	6	8
Vigorous	3	6	9	12

Appendix B: Participant consent and assent forms

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EXERCISE METABOLISM RESEARCH GROUP
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INFORMATION & CONSENT TO PARTICIPATE IN RESEARCH

THE ACUTE EFFECTS OF MODERATE INTENSITY CYCLING EXERCISE ON VASCULAR FUNCTION IN INDIVIDUALS WITH REPAIRED COARCTATION OF THE AORTA

Study sponsored by NSERC Canada.

You are being invited to participate in a research study being conducted by the investigators listed below. Prior to participating in this study you are asked to read this form, which outlines the purpose and testing procedures used in this study and the potential risks and benefits. Once you understand the study, you will be asked to sign this form if you wish to participate. Unless otherwise stated, all testing and experimental procedures will be conducted in the Exercise Metabolism Research Laboratory, Rm. A103, Ivor Wynne Centre.

INVESTIGATOR:	DEPARTMENT:	CONTACT:
Dr. Maureen MacDonald	Kinesiology, IWC 212	x23580
Dr. Rejane Dillenburg	Hamilton Health Sciences, Pediatrics, HSC-2F17	x75242
Nicole Proudfoot	Kinesiology, IWC AB132	x27384

PURPOSE:
The purpose of this study is to see the effect of a short session of moderate intensity cycling exercise on arm and leg blood vessel function in young, healthy humans and young adults with previous correction of a congenital heart abnormality (coarctation of the aorta). In coarctation of the aorta, a portion of the aorta (the blood vessel coming off the heart) is abnormally narrow. This results in high blood pressure in the upper limbs, head and neck and low blood pressure and blood flow in the lower body. Surgery is performed in most patients. This often reduces or eliminates the resting blood pressure symptoms yet some people have lasting changes to their heart and blood vessels. Further study and alternative treatment development is required. This study will examine the acute effects of moderate exercise with a goal of providing information for the development of exercise training programs as a way to improve heart and blood vessel function in this patient population.

DESCRIPTION OF TESTING PROCEDURES:
You will be required to visit the lab two different times and perform the following exercises:
(A) Leg cycling exercise
(B) Arm cycling exercise

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Leg cycling exercise: You will perform leg cycling on a stationary bicycle (cycle ergometer) at a moderate intensity for 20 minutes. Your heart rate will be monitored during the exercise. You may voluntarily stop at any point during the exercise.

Arm cycling exercise: Similar to the leg cycling exercise except performed on an arm cycle ergometer.

Before and after arm and leg exercise the following measurements will be taken:

Blood Pressure: Blood pressure will be measured by two different methods. The first requires the placement of a small cuff around the arm. Blood pressure is measured automatically several times. The second technique involves holding a flat topped, pen-like pressure instrument .on your neck.

Heart Rate: Six spot electrodes on the skin surface of the chest will monitor heart rate.

Blood vessel stiffness: This procedure uses a both blood pressure and ultrasound measurements. You will be lying down when this procedure is done. A technician will take pictures of the blood vessel in your neck (carotid artery) using a wand-like instrument. At the same time another technician will obtain blood pressure measurements using the pen-like probe on the other side of your neck. This measurement will also be done on the leg at the back of the knee (popliteal artery) and arm at your elbow (brachial artery). We will also measure blood vessel stiffness by placing 2 of the pen-like probes on the artery and seeing how long it takes the pulse to travel down the artery.

Arterial Reactivity: A blood pressure cuff around the forearm or lower leg is inflated to a pressure of approximately 200mmHg, which cuts off arm or leg blood flow. The cuff is held inflated for 5 minutes. When the cuff is released there is an increase in blood flow and changes in artery diameter. This is measured using Ultrasound in the same way as blood vessel stiffness (described above). This procedure does cause discomfort but any discomfort is quickly relieved when the cuff is released. There is no danger from this experimental procedure unless the cuff is left inflated for very long periods (over 45 minutes).

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POTENTIAL RISKS AND DISCOMFORTS:
All procedures are non invasive and offer minimal risk to you. In rare instances, participants may experience brief numbness and or tingling in the limb when blood flow is stopped and immediately following release of the cuff and a minor rash from electrode adhesive and or gel. There is no known medical risk associated with a 5 minute period of blood flow stoppage to the hand or foot and there is no lasting effect of this on the function of the limbs.

BENEFITS:
In participating in this project you realize that there are no direct benefits to you. However, the information gained from this study will benefit the scientific community and society by increasing our knowledge of how blood vessels adapt to acute exercise. It may lead to a better understanding of how exercise can be used to improve cardiovascular function in people with coarctation of the aorta.

CONFIDENTIALITY:
All data collected during this study will remain confidential and stored in offices and on computers to which only the investigator has access. You should be aware that the results of this study will be made available to the scientific community through publication in a scientific journal. Neither your name nor any reference to you will be used in publishing these results.

PARTICIPATION & WITHDRAWL
You can choose whether or not to participate in this study. You should be aware that your participation in this study would in no way affect your academic performance in any course offered within the Department of Kinesiology. You have the option of removing your data from the study if you wish. You may also refuse to answer any questions posed to you during the study and still remain as a participant in the study.

RIGHTS OF RESEARCH PARTICIPANTS
You will receive a signed copy of this ethics form. You may withdraw your consent to participate in this study at any time. You may also discontinue participation at any time without penalty. In signing this consent form or in participating in this study you are not waiving any legal claims or remedies. This study has been reviewed and received clearance from the Hamilton Health Sciences/Faculty of Healthy Sciences Research Ethics Board. If you have any questions regarding your rights as a research participant please contact the Office of the REB Chair of the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board at 905-521-2100, Ext. 42013.

INFORMATION:
You will be able to contact Nicole Proudfoot at 905-525-9140 (x27384) or Dr. MacDonald at 905-525-9140 (x23580) regarding any questions about the study.

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I HAVE READ AND UNDERSTAND THE ABOVE EXPLANATION OF THE PURPOSE AND PROCEDURES OF THE PROJECT. I HAVE ALSO READ AND COMPLETED THE ATTACHED FORM ENTITLED "SUBJECT SCREENING QUESTIONNAIRE" AND AGREE TO PARTICIPATE/ALLOW MY CHILD TO PARTICIPATE AS A SUBJECT. I HAVE ALSO RECEIVED A SIGNED COPY OF THE INFORMATION AND CONSENT FORM. MY QUESTIONS HAVE BEEN ANSWERED TO MY SATISFACTION AND I AGREE TO PARTICIPATE IN THIS STUDY. I WILL RECEIVE A SIGNED COPY.

Printed name of participant	Date
Printed name of legally authorized representative	Date
Signature of participant/legally authorized representative	Date
Printed name of person obtaining consent	Date
Signature of person obtaining consent	Date

INVESTIGATOR

In my judgement the participant is voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent and participate in this research study.

Printed name of investigator	Date
Signature of investigator	Date

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EXERCISE METABOLISM RESEARCH GROUP
DEPARTMENT OF KINESIOLOGY, MCMASTER UNIVERSITY

INFORMATION & ASSENT TO PARTICIPATE IN RESEARCH

THE ACUTE EFFECTS OF MODERATE INTENSITY CYCLING EXERCISE ON VASCULAR FUNCTION IN INDIVIDUALS WITH REPAIRED COARCTATION OF THE AORTA

Study sponsored by NSERC Canada.

You have been asked to take part in a project being conducted by the people listed below. Before you agree to take part, you are asked to read this form which will tells you what you will have to do if you take part and if there is any chance you might be hurt. You can ask as many questions as you wish. Once you understand the study, you will be asked to sign this form if you wish to participate. The testing will take place in the Exercise Metabolism Research Laboratory, Rm. A103, Ivor Wynne Centre, McMaster University.

INVESTIGATOR:	DEPARTMENT:	CONTACT:
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Why are we doing this study?
The point of this study is to look at what exercise does to blood vessels in children with repaired coarctation of the aorta.

What if I have questions?
You can ask questions if do you do not understand any part of the study. If you have questions later that you don't think of now, you can talk to me again or call one of the investigators listed above.

If I am in the study what will happen to me?
If you decide that you want to be part of this study, you will be asked to come into the laboratory for two visits. When you come in you will lie on a bed and rest for about 15 minutes. At the end of the 15 minutes we will measure your pulse in your neck, groin, wrist, and foot using pen-like devices touching your skin. We will also take a picture of the artery in your neck using an ultrasound machine. This is the same machine that doctors use to take a picture of a baby during pregnancy. After this, you will cycle for 20 minutes. On one day you will cycle with your legs and the other with your arms. After the exercise you will lie back on the bed for 45 minutes and we will do all the same measurements again (pulse, ultrasound). The whole visit will take about 2 hours.

McMaster University

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Will I be hurt if I am in the study?
There are some things about this study you should know. You may feel a little tired after the exercise test, but this feeling won't last long. You might also get bored when you are lying on the bed or exercising. You can listen to music or watch a movie while you are exercising. If you have coarctation of the aorta, a doctor will be in the room when you are exercising in case it causes you problems, but this is unlikely.

Will the study help me?
If you are in the study it may not help or benefit you. The study may help us to understand what happens to blood vessels after we exercise so that in the future we can tell people what exercises help them the most.

Do I have to be in this study?
You do not have to be in this study, if you do not want to be. If you decide that you don't want to be in the study after we begin, that's OK too. Nobody will be angry or upset. We are discussing the study with your parent/guardian and you should talk to them about it too.

What happens after the study?
When we are finished this study we will write a report about what was learned. This report will not include your name or that you were in the study.

Assent:
If you decide you want to be in this study, please print/write your name. If you decide that you don't want to be in the study, even if you have started in the study, then all you have to do is tell the on of the investigators listed above (MacDonald, Dillenburg, Proudfoot).

I,_____ (Print your name) would like to be in this research study.

_____ (Date of assent)

_____ (Name of person who obtained assent)

_____ (Signature of person who obtained assent and Date)

_____ (Local Principal Investigator name)

_____ (LPI signature and Date)

Appendix C: Data and t-test tables – Participant characteristics

C.1 Age

	Age (y)		Sex
	CoA	Control	
1	16	16	M
2	10	10	M
3	8	7	M
4	8	8	M
5	10	10	M
6	16	14	F
7	11	10	F
8	15	15	M
9	13	12	M
Mean	**12**	**11**	
SD	3	3	

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	11.888	3.216	1.072
CON	9	0	11.333	3.122	1.041

Difference 0.555

t = 0.371 with 16 degrees of freedom. (P = 0.715)

C.2 CoA: Age at time of repair and years since repair

	Age at Repair (y)	Years Since Repair
1	9	6
2	3	5
3	0.3	7
4	0.1	8
5	0.1	10
6	2	13
7	2.5	9
8	0.1	15
9	6	7
Mean	**3**	**9**
Median	**2**	**8**
SD	3	3

C.3 Height and weight

	Height (m)		Weight (kg)	
	CoA	Control	CoA	Control
1	1.75	1.75	64.4	69.5
2	1.33	1.38	49.9	36.5
3	1.30	1.23	29.6	22.5
4	1.48	1.23	48.0	23.0
5	1.45	1.50	54.9	37.9
6	1.57	1.73	56.2	61.4
7	1.51	1.31	53.3	28.2
8	1.65	1.74	48.6	64.0
9	1.51	1.62	38.4	33.8
Mean	**1.50**	**1.50**	**49.2**	**41.9**
SD	0.14	0.22	10.2	18.2

Height: **T-test for independent samples**

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	1.504	0.141	0.0471
CON	9	0	1.498	0.221	0.0736
Difference	0.00668				

t = 0.0765 with 16 degrees of freedom. (P = 0.940)

Weight: **T-test for independent samples**

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	49.244	10.203	3.401
CON	9	0	41.867	18.243	6.081
Difference	7.378				

t = 1.059 with 16 degrees of freedom. (P = 0.305)

C.4 BMI and BMI percentile

	BMI (kg/m2)		BMI %ile	
	CoA	Control	CoA	Control
1	21.1	22.7	66	73
2	28.2	19.0	> 95	89
3	17.5	15.0	88	34
4	22.1	15.3	> 95	43
5	26.1	16.8	> 95	54
6	22.8	20.5	77	63
7	23.4	16.6	91	37
8	17.9	21.1	18	66
9	16.8	12.9	21	5
Mean	**21.8**	**17.8**	**72**	**52**
SD	3.9	3.3	33	25

BMI: **T-test for independent samples**

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	21.763	3.912	1.304
CON	9	0	17.776	3.255	1.085
Difference	3.988				

t = 2.350 with 16 degrees of freedom. (P = 0.032)

BMI percentile: **T-test for independent samples**

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	71.778	31.188	10.396
CON	9	0	51.556	24.920	8.307
Difference	20.222				

t = 1.520 with 16 degrees of freedom. (P = 0.148)

Appendix D: Data and t-test tables – Baseline heart rate and blood pressure

D.1 Heart Rate (bpm)

	CoA	Control
1	56	64
2	90	74
3	98	74
4	82	77
5	51	70
6	62	82
7	91	75
8	67	61
9	75	67
Mean	**75**	**72**
SD	17	7

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	74.531	16.568	5.523
CON	9	0	71.509	6.663	2.221
Difference	3.022				

t = 0.508 with 16 degrees of freedom. (P = 0.619)

Test execution ended by user request, Rank Sum Test begun

Mann-Whitney Rank Sum Test

Group	N	Missing	Median	25%	75%
COA	9	0	74.850	60.316	89.823
CON	9	0	74.115	65.906	75.245

T = 92.000 n(small)= 9 n(big)= 9 (P = 0.596)

D.2 Brachial systolic blood pressure (mmHg)

	CoA	Control
1	113	119
2	102	104
3	118	97
4	118	100
5	105	106
6	100	108
7	115	98
8	111	108
9	107	105
Mean	**110**	**105**
SD	7	7

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	109.722	6.778	2.259
CON	9	0	104.931	6.688	2.229

Difference 4.792

t = 1.510 with 16 degrees of freedom. (P = 0.151)

D.3 Brachial diastolic blood pressure (mmHg)

	CoA	Control
1	55	55
2	48	49
3	64	51
4	64	50
5	45	55
6	45	53
7	53	50
8	55	51
9	54	64
Mean	**54**	**53**
SD	7	5

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	53.611	6.999	2.333
CON	9	0	52.963	4.787	1.596

Difference 0.648

t = 0.229 with 16 degrees of freedom. (P = 0.822)

D.4 Brachial mean arterial pressure (mmHg)

	CoA	Control
1	74	76
2	66	67
3	82	66
4	82	66
5	65	72
6	63	71
7	74	66
8	74	70
9	72	78
Mean	**72**	**70**
SD	7	4

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	72.315	6.772	2.257
CON	9	0	70.285	4.462	1.487

Difference 2.029

t = 0.751 with 16 degrees of freedom. (P = 0.464)

D.5 Brachial pulse pressure (mmHg)

	CoA	Control
1	57	64
2	54	56
3	55	46
4	54	50
5	60	51
6	55	55
7	62	49
8	56	56
9	53	41
Mean	**56**	**52**
SD	3	7

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	56.111	3.082	1.027
CON	9	0	51.968	6.801	2.267

Difference 4.144

t = 1.665 with 16 degrees of freedom. (P = 0.115)

D.6 Popliteal systolic blood pressure (mmHg)

	CoA	Control
1	126	115
2	106	113
3	113	100
4	129	105
5	111	118
6	120	124
7	118	104
8	103	115
9	106	123
Mean	**114**	**113**
SD	9	8

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	114.454	9.133	3.044
CON	9	0	112.972	8.342	2.781
Difference	1.481				

t = 0.359 with 16 degrees of freedom. (P = 0.724)

D.7 Popliteal diastolic blood pressure (mmHg)

	CoA	Control
1	51	51
2	48	50
3	55	44
4	58	50
5	50	52
6	57	55
7	53	49
8	48	50
9	52	59
Mean	**52**	**51**
SD	3	4

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	52.435	3.428	1.143
CON	9	0	50.861	4.085	1.362
Difference	1.574				

t = 0.885 with 16 degrees of freedom. (P = 0.389)

D.8 Popliteal mean arterial pressure (mmHg)

	CoA	Control
1	76	72
2	67	71
3	74	63
4	81	68
5	70	74
6	78	78
7	75	67
8	67	72
9	70	80
Mean	**73**	**72**
SD	5	5

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	73.108	4.916	1.639
CON	9	0	71.565	5.330	1.777
Difference	1.543				

t = 0.639 with 16 degrees of freedom. (P = 0.532)

D.9 Popliteal pulse pressure (mmHg)

	CoA	Control
1	75	65
2	57	63
3	58	56
4	71	55
5	61	67
6	63	69
7	65	56
8	55	65
9	54	64
Mean	**62**	**62**
SD	7	5

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	62.019	7.187	2.396
CON	9	0	62.167	5.085	1.695
Difference	-0.148				

t = -0.0505 with 16 degrees of freedom. (P = 0.960)

D.10 Arm-leg gradient (mmHg)

	CoA	Control
1	-13	4
2	-4	-9
3	6	-4
4	-11	-5
5	-7	-12
6	-21	-16
7	-3	-6
8	7	-7
9	2	-18
Mean	**-5**	**-8**
SD	9	7

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	-4.731	9.105	3.035
CON	9	0	-8.042	6.536	2.179
Difference	3.310				

t = 0.886 with 16 degrees of freedom. (P = 0.389)

Appendix E: Data and t-test tables – Baseline carotid artery variables

E.1 Carotid pulse pressure (mmHg)

	CoA	Control
1	31	37
2	43	35
3	42	21
4	36	29
5	31	27
6	34	34
7	35	29
8	47	36
9	29	27
Mean	**36**	**31**
SD	6	5

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	36.471	6.183	2.061
CON	9	0	30.552	5.339	1.780
Difference	5.919				

t = 2.174 with 16 degrees of freedom. (P = 0.045)

E.2 Carotid artery minimum lumen diameter (mm)

	CoA	Control
1	5.8	5.9
2	5.7	5.8
3	5.8	5.0
4	6.8	5.3
5	6.8	5.5
6	5.7	5.1
7	5.5	5.3
8	6.7	5.5
9	6.3	5.1
Mean	**6.1**	**5.4**
SD	0.5	0.3

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	6.116	0.519	0.173
CON	9	0	5.386	0.302	0.101
Difference	0.730				

t = 3.647 with 16 degrees of freedom. (P = 0.002)

E.3 Carotid artery maximum lumen diameter (mm)

	CoA	Control
1	6.6	6.6
2	6.6	6.5
3	6.9	5.9
4	7.6	6.0
5	8.1	6.2
6	6.5	5.7
7	6.4	6.2
8	7.6	6.2
9	6.8	5.7
Mean	**7.0**	**6.1**
SD	0.6	0.3

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	7.021	0.607	0.202
CON	9	0	6.112	0.318	0.106
Difference	0.909				

t = 3.978 with 16 degrees of freedom. (P = 0.001)

D.13 Carotid artery mean lumen diameter (mm)

	CoA	Control
1	6.2	6.2
2	6.1	6.1
3	6.3	5.5
4	7.2	5.7
5	7.4	5.9
6	6.2	5.7
7	5.9	5.9
8	7.2	5.8
9	6.5	5.4
Mean	**6.5**	**5.8**
SD	0.6	0.3

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	6.543	0.555	0.185
CON	9	0	5.793	0.269	0.0895
Difference	0.751				

t = 3.655 with 16 degrees of freedom. (P = 0.002)

E.4 Carotid artery intima media thickness (mm)

	CoA	Control
1	0.42	0.39
2	0.43	0.43
3	0.42	0.39
4	0.43	0.39
5	0.46	0.42
6	0.38	0.43
7	0.40	0.45
8	0.58	0.44
9	0.43	0.48
Mean	**0.44**	**0.42**
SD	0.06	0.03

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	0.438	0.0573	0.0191
CON	9	0	0.424	0.0310	0.0103

Difference 0.0139

t = 0.641 with 16 degrees of freedom. (P = 0.530)

Appendix F: Data and t-test tables – Baseline arterial stiffness

F.1 Carotid artery distensibility ($mmHg^{-1}$)

	CoA	Control
1	0.0095	0.0072
2	0.0089	0.0081
3	0.0092	0.0203
4	0.0079	0.0094
5	0.0141	0.0106
6	0.0096	0.0072
7	0.0099	0.0127
8	0.0059	0.0072
9	0.0085	0.0086
Mean	**0.0093**	**0.0102**
SD	0.0022	0.0042

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	0.00928	0.00217	0.000725
CON	9	0	0.0102	0.00424	0.00141
Difference	-0.000868				

t = -0.547 with 16 degrees of freedom. (P = 0.592)

F.2 Central pulse wave velocity (m/s)

	CoA	Control
1	3.1	2.7
2	-------	-------
3	2.7	2.2
4	2.4	2.2
5	2.6	3.3
6	2.6	2.4
7	3.0	2.3
8	2.6	2.5
9	2.4	2.7
Mean	**2.7**	**2.5**
SD	0.3	0.4

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	8	0	2.683	0.264	0.0933
CON	8	0	2.520	0.367	0.130
Difference	0.163				

t = 1.020 with 14 degrees of freedom. (P = 0.325)

F.3 Upper limb pulse wave velocity (m/s)

	CoA	Control
1	6.5	5.6
2	-------	-------
3	6.7	7.9
4	6.5	7.0
5	5.7	6.4
6	6.6	7.0
7	5.7	6.3
8	5.8	5.9
9	5.4	8.2
Mean	**6.1**	**6.8**
SD	0.5	0.9

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	8	0	6.100	0.498	0.176
CON	8	0	6.796	0.909	0.321
Difference	-0.696				

t = -1.899 with 14 degrees of freedom. (P = 0.078)

F.4 Lower limb pulse wave velocity (m/s)

	CoA	Control
1	7.0	5.0
2	-------	-------
3	6.0	7.2
4	10.9	7.5
5	5.0	7.0
6	6.8	6.3
7	7.1	6.0
8	7.6	7.0
9	7.9	7.8
Mean	**7.3**	**6.7**
SD	1.7	0.9

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	8	0	7.297	1.738	0.614
CON	8	0	6.726	0.934	0.330
Difference	0.570				

t = 0.817 with 14 degrees of freedom. (P = 0.428)

F.3 Upper versus lower limb pulse wave velocity (m/s)

CoA:

	Upper limb PWV	Lower limb PWV
1	6.5	7.0
2	-------	-------
3	6.7	6.0
4	6.5	10.9
5	5.7	5.0
6	6.6	6.8
7	5.7	7.1
8	5.8	7.6
9	5.4	7.9
Mean	**6.1**	**7.3**
SD	0.5	1.7

T-test for dependent samples

Treatment Name	N	Missing	Mean	Std Dev	SEM
UPPER LIMB	8	0	6.100	0.498	0.176
LOWER LIMB	8	0	7.297	1.738	0.614
Difference	8	0	-1.197	1.739	0.615

t = -1.946 with 7 degrees of freedom. (P = 0.093)

Control:

	Upper limb PWV	Lower limb PWV
1	5.6	5.0
2	-------	-------
3	7.9	7.2
4	7.0	7.5
5	6.4	7.0
6	7.0	6.3
7	6.3	6.0
8	5.9	7.0
9	8.2	7.8
Mean	**6.8**	**6.7**
SD	0.9	0.9

T-test for dependent samples

Treatment Name	N	Missing	Mean	Std Dev	SEM
UPPER LIMB	8	0	6.796	0.909	0.321
LOWER LIMB	8	0	6.726	0.934	0.330
Difference	8	0	0.0691	0.701	0.248

t = 0.279 with 7 degrees of freedom. (P = 0.788)

Appendix G: Data and t-test tables – Overweight/at risk versus healthy weight (within CoA)

G.1 Carotid artery mean lumen diameter (mm)

Overweight		Healthy weight	
3	6.3	**9**	6.5
4	7.2	**6**	6.2
2	6.1	**8**	7.2
5	7.4	**1**	6.2
7	5.9	---	-------
Mean	6.6	**Mean**	6.5
SD	0.7	**SD**	0.5
Range	5.9-7.2	**Range**	6.2-7.2

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
Overweight	5	0	6.579	0.666	0.298
Normal weight	4	0	6.499	0.473	0.237
Difference	0.0804				

t = 0.203 with 7 degrees of freedom. (P = 0.845)

G.2 Carotid artery pulse pressure (mmHg)

Overweight		Healthy weight	
3	42	**9**	29
4	36	**6**	34
2	43	**8**	47
5	31	**1**	31
7	35	---	-------
Mean	37	**Mean**	35
SD	5	**SD**	8
Range	31-43	**Range**	29-46

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
Overweight	5	0	37.498	5.060	2.263
Normal weight	4	0	35.188	7.992	3.996
Difference	2.310				

t = 0.531 with 7 degrees of freedom. (P = 0.612)

G.3 Upper limb pulse wave velocity (m/s)

Overweight		Healthy weight	
3	6.7	**9**	5.4
4	6.5	**6**	6.6
2	-------	**8**	5.8
5	5.7	**1**	6.5
7	5.7	---	-------
Mean	6.1	**Mean**	6.1
SD	0.5	**SD**	0.6
Range	5.7-6.7	**Range**	5.4-6.6

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
Overweight	4	0	6.144	0.511	0.256
Normal weight	4	0	6.055	0.559	0.280
Difference	0.0885				

t = 0.234 with 6 degrees of freedom. (P = 0.823)

Appendix H: Parent-reported activity

	Active		Sedentary	
	CoA	**Control**	**CoA**	**Control**
1	14	12	5	5
2	15	9	5	6
3	14	16	4	4
4	19	11	4	5
5	14	12	4	5
6	4	4	7	6
7	19	19	6	2
8	6	10	9	4
9	16	12	8	5
Mean	**13**	**12**	**6**	**5**
SD	5	4	2	1

Physical activities

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	13.444	5.199	1.733
CON	9	0	11.667	4.213	1.404
Difference	1.778				

t = 0.797 with 16 degrees of freedom. (P = 0.437)

Sedentary activities

T-test for independent samples

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	5.778	1.856	0.619
CON	9	0	4.667	1.225	0.408
Difference	1.111				

t = 1.499 with 16 degrees of freedom. (P = 0.153)

Appendix I: Raw baseline data tables

I.1 Baseline heart rate

	HR					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	58	53	56	63	64	64
2	90	89	90	78	71	74
3	97	99	98	73	76	74
4	82	82	82	76	78	77
5	52	51	51	68	72	70
6	65	59	62	89	74	82
7	91	90	91	72	77	75
***8**	64	69	67	62	60	61
9	72	77	75	70	63	67
Mean	**75**	**74**	**75**	**72**	**71**	**72**
SD	16	17	17	8	7	7

I.2 Baseline brachial systolic blood pressure

	Brachial SBP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	116	110	113	114	124	119
2	105	99	102	103	106	104
3	120	117	118	92	102	97
4	120	116	118	99	101	100
5	107	102	105	105	107	106
6	103	97	100	109	108	108
7	115	115	115	102	95	98
***8**	109	113	111	110	106	108
9	108	106	107	104	106	105
Mean	**111**	**108**	**110**	**104**	**106**	**105**
SD	6	8	7	7	8	7

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.3 Baseline brachial diastolic blood pressure

	Brachial DBP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	57	54	55	54	56	55
2	53	44	48	58	40	49
3	63	65	64	52	50	51
4	68	59	64	51	49	50
5	44	46	45	58	52	55
6	47	43	45	54	52	53
7	54	52	53	52	47	50
***8**	54	56	55	57	46	51
9	58	51	54	61	68	64
Mean	**55**	**52**	**54**	**55**	**51**	**53**
SD	7	7	7	3	8	5

I.4 Baseline brachial mean arterial pressure

	Brachial MAP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	77	72	74	74	79	76
2	70	62	66	73	62	67
3	82	82	82	65	67	66
4	85	78	82	67	66	66
5	65	64	65	73	70	72
6	66	61	63	72	71	71
7	74	73	74	69	63	66
***8**	72	75	74	74	66	70
9	75	69	72	75	80	78
Mean	**74**	**71**	**72**	**71**	**69**	**70**
SD	7	7	7	4	6	4

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.5 Baseline brachial pulse pressure

	Brachial PP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	59	56	57	61	68	64
2	52	56	54	45	66	56
3	57	53	55	40	53	46
4	52	57	54	48	52	50
5	64	57	60	48	55	51
6	56	54	55	55	56	55
7	61	63	62	50	48	49
***8**	55	57	56	60	53	56
9	50	56	53	43	39	41
Mean	**56**	**56**	**56**	**50**	**54**	**52**
SD	4	3	3	7	9	7

I.6 Baseline popliteal systolic blood pressure

	Popliteal SBP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	124	127	126	111	120	115
2	114	98	106	112	114	113
3	105	120	113	105	96	100
4	129	129	129	108	101	105
5	107	116	111	118	118	118
6	119	122	120	124	125	124
7	124	112	118	111	98	104
***8**	104	103	103	115	115	115
9	106	105	106	124	121	123
Mean	**114**	**115**	**114**	**114**	**112**	**113**
SD	9	11	9	7	11	8

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.7 Baseline popliteal diastolic pressure

	Popliteal DBP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	50	52	51	49	53	51
2	56	41	48	53	47	50
3	49	61	55	46	43	44
4	62	54	58	53	46	50
5	50	50	50	53	50	52
6	59	56	57	52	58	55
7	53	53	53	50	48	49
***8**	50	47	48	53	48	50
9	53	52	52	57	61	59
Mean	**53**	**52**	**52**	**52**	**50**	**51**
SD	4	6	3	3	6	4

I.8 Baseline popliteal mean arterial pressure

	Popliteal MAP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	75	77	76	69	75	72
2	75	60	67	73	69	71
3	67	81	74	65	60	63
4	84	79	81	71	64	68
5	69	72	70	75	73	74
6	79	78	78	76	80	78
7	77	73	75	70	64	67
***8**	68	65	67	73	70	72
9	70	69	70	79	81	80
Mean	**74**	**73**	**73**	**72**	**71**	**72**
SD	5	7	5	4	7	5

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.9 Baseline popliteal pulse pressure

	Popliteal PP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	74	75	75	63	67	65
2	58	57	57	59	67	63
3	57	59	58	60	53	56
4	67	76	71	55	55	55
5	57	66	61	65	68	67
6	60	67	63	72	67	69
7	71	59	65	61	51	56
***8**	53	57	55	63	67	65
9	54	54	54	67	61	64
Mean	**61**	**63**	**62**	**63**	**62**	**62**
SD	8	8	7	5	7	5

I.10 Baseline arm-leg systolic blood pressure gradient

	Arm-Leg SBP Gradient					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	-9	-18	-13	3	5	4
2	-9	2	-4	-10	-9	-9
3	15	-3	6	-14	7	-4
4	-9	-14	-11	-10	-1	-5
5	0	-14	-7	-13	-12	-12
6	-16	-26	-21	-15	-17	-16
7	-9	4	-3	-9	-3	-6
***8**	5	10	7	-6	-9	-7
9	2	1	2	-20	-15	-18
Mean	**-3**	**-6**	**-5**	**-10**	**-6**	**-8**
SD	9	12	9	6	9	7

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.11 Baseline carotid pulse pressure

	Carotid PP					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	35	28	31	33	42	37
2	41	45	43	33	37	35
3	45	40	42	23	19	21
4	33	39	36	29	28	29
5	32	31	31	28	26	27
6	32	36	34	33	35	34
7	33	36	35	31	28	29
***8**	44	49	47	33	39	36
9	26	32	29	29	25	27
Mean	**36**	**37**	**36**	**30**	**31**	**31**
SD	6	7	6	3	7	5

I.12 Baseline minimum lumen diameter

	LD Minimum					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	5.8	5.8	5.8	5.8	6.0	5.9
2	5.7	5.7	5.7	5.9	5.7	5.8
3	5.9	5.7	5.8	5.1	4.9	5.0
4	6.8	6.7	6.8	5.3	5.4	5.3
5	6.9	6.7	6.8	5.3	5.6	5.5
6	5.7	5.7	5.7	5.3	5.0	5.1
7	5.5	5.6	5.5	5.3	5.3	5.3
***8**	6.7	6.7	6.7	5.6	5.3	5.5
9	6.6	5.9	6.3	4.9	5.4	5.1
Mean	**6.2**	**6.1**	**6.1**	**5.4**	**5.4**	**5.4**
SD	0.6	0.5	0.5	0.3	0.3	0.3

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.13 Baseline maximum carotid lumen diameter

	LD Maximum					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	6.7	6.5	6.6	6.6	6.6	6.6
2	6.6	6.7	6.6	6.6	6.5	6.5
3	7.0	6.7	6.9	6.0	5.8	5.9
4	7.7	7.6	7.6	6.0	6.0	6.0
5	8.2	8.1	8.1	6.0	6.4	6.2
6	6.7	6.4	6.5	5.9	5.6	5.7
7	6.4	6.4	6.4	6.2	6.2	6.2
***8**	7.6	7.6	7.6	6.4	6.0	6.2
9	7.1	6.5	6.8	5.5	5.9	5.7
Mean	**7.1**	**6.9**	**7.0**	**6.1**	**6.1**	**6.1**
SD	0.6	0.6	0.6	0.3	0.3	0.3

I.14 Baseline mean carotid lumen diameter

	LD Mean					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	6.2	6.1	6.2	6.1	6.3	6.2
2	6.1	6.2	6.1	6.2	6.1	6.1
3	6.4	6.2	6.3	5.6	5.3	5.5
4	7.2	7.2	7.2	5.6	5.7	5.7
5	7.4	7.4	7.4	5.7	6.0	5.9
6	6.2	6.1	6.2	5.5	5.3	5.4
7	5.9	5.9	5.9	5.7	5.7	5.7
***8**	7.2	7.1	7.2	6.0	5.7	5.8
9	6.8	6.3	6.5	5.2	5.6	5.4
Mean	**6.6**	**6.5**	**6.5**	**5.7**	**5.8**	**5.7**
SD	0.6	0.6	0.6	0.3	0.3	0.3

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.15 Baseline carotid intima media thickness

	IMT					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	0.41	0.42	0.42	0.39	0.39	0.39
2	0.43	0.43	0.43	0.43	0.43	0.43
3	0.40	0.43	0.42	0.39	0.39	0.39
4	0.40	0.46	0.43	0.40	0.39	0.39
5	0.49	0.44	0.46	0.43	0.40	0.42
6	0.38	0.37	0.38	0.40	0.46	0.43
7	0.38	0.42	0.40	0.40	0.50	0.45
***8**	0.56	0.59	0.58	0.43	0.44	0.44
9	0.43	0.44	0.43	0.51	0.46	0.48
Mean	**0.43**	**0.44**	**0.44**	**0.42**	**0.43**	**0.42**
SD	0.06	0.06	0.06	0.04	0.04	0.03

I.16 Baseline carotid distensibility

	Distensibility					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	0.0095	0.0096	0.0095	0.0092	0.0052	0.0072
2	0.0088	0.0091	0.0089	0.0080	0.0081	0.0081
3	0.0089	0.0095	0.0092	0.0178	0.0229	0.0203
4	0.0083	0.0075	0.0079	0.0099	0.0089	0.0094
5	0.0129	0.0154	0.0141	0.0103	0.0109	0.0106
6	0.0112	0.0079	0.0096	0.0074	0.0071	0.0072
7	0.0110	0.0087	0.0099	0.0122	0.0132	0.0127
***8**	0.0062	0.0056	0.0059	0.0075	0.0069	0.0072
9	0.0085	0.0084	0.0085	0.0094	0.0078	0.0086
Mean	**0.0095**	**0.0091**	**0.0093**	**0.0102**	**0.0101**	**0.0102**
SD	0.0020	0.0027	0.0022	0.0032	0.0053	0.0042

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.17 Baseline central pulse wave velocity

	Central PWV					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	3.2	3.0	3.1	2.6	2.7	2.7
2	---	---	---	---	---	---
3	2.8	2.6	2.7	2.1	2.2	2.2
4	2.4	2.3	2.4	2.2	2.2	2.2
5	2.6	2.6	2.6	3.2	3.4	3.3
6	2.7	2.5	2.6	2.3	2.4	2.4
7	3.1	3.0	3.0	2.3	2.2	2.3
***8**	2.8	2.5	2.6	2.5	2.5	2.5
9	2.2	2.7	2.4	2.8	2.6	2.7
Mean	**2.7**	**2.7**	**2.7**	**2.5**	**2.5**	**2.5**
SD	0.3	0.2	0.3	0.4	0.4	0.4

I.18 Baseline upper limb pulse wave velocity

	Upper Limb PWV					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	6.8	6.1	6.5	5.7	5.5	5.6
2	---	---	---	---	---	---
3	6.5	6.8	6.7	8.0	7.9	7.9
4	6.1	6.9	6.5	7.5	6.5	7.0
5	5.9	5.5	5.7	6.9	5.8	6.4
6	6.6	6.6	6.6	6.5	7.5	7.0
7	5.5	5.9	5.7	6.3	6.2	6.3
***8**	5.6	6.0	5.8	6.2	5.7	5.9
9	5.2	5.5	5.4	8.3	8.1	8.2
Mean	**6.0**	**6.2**	**6.1**	**6.9**	**6.7**	**6.8**
SD	0.6	0.5	0.5	0.9	1.0	0.9

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

I.19 Baseline lower limb pulse wave velocity

	Lower Limb PWV					
	CoA			Control		
	Day 1	**Day 2**	**Average**	**Day 1**	**Day 2**	**Average**
1	7.4	6.6	7.0	4.9	5.0	5.0
2	---	---	---	---	---	---
3	4.6	7.4	6.0	8.0	6.3	7.2
4	10.8	11.0	10.9	7.6	7.4	7.5
5	4.8	5.1	5.0	6.4	7.7	7.0
6	6.8	6.8	6.8	6.6	6.1	6.3
7	7.2	7.0	7.1	6.8	5.2	6.0
***8**	6.8	8.5	7.6	7.1	6.9	7.0
9	9.6	6.2	7.9	7.1	8.5	7.8
Mean	**7.3**	**7.3**	**7.3**	**6.8**	**6.6**	**6.7**
SD	2.1	1.8	1.7	1.0	1.2	0.9

** Subject 8 in both groups performed leg and arm exercise tests on the same day*

Appendix J Data and t-test tables – Heart rate during exercise

J.1 Heart Rate – Leg exercise

	Average HR		Peak HR	
	CoA	**Control**	**CoA**	**Control**
1	88	102	108	119
2	130	112	170	139
3	133	120	145	145
4	123	122	145	141
5	96	124	115	145
6	94	137	119	151
7	141	125	171	146
8	115	90	130	113
9	107	101	123	119
Mean	**114**	**115**	**136**	**135**
SD	19	15	23	14

Average HR: **T-test for independent samples**

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	114.137	18.952	6.317
CON	9	0	114.689	14.690	4.897
Difference	-0.552				

t = -0.0691 with 16 degrees of freedom. (P = 0.946)

Peak HR: **T-test for independent samples**

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	136.222	22.981	7.660
CON	9	0	135.256	14.332	4.777
Difference	0.967				

t = 0.107 with 16 degrees of freedom. (P = 0.916)

J.2 Heart Rate – Arm exercise

	Average HR		Peak HR	
	CoA	**Control**	**CoA**	**Control**
1	87	98	108	121
2	122	109	139	128
3	135	114	154	140
4	118	116	134	140
5	83	112	101	134
6	113	122	133	143
7	138	122	162	148
8	118	99	141	111
9	117	104	158	120
Mean	**115**	**111**	**137**	**132**
SD	19	9	21	12

Average HR: **T-test for independent samples**

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	114.571	18.896	6.299
CON	9	0	110.613	8.960	2.987
Difference	3.958				

t = 0.568 with 16 degrees of freedom. (P = 0.578)

Peak HR: **T-test for independent samples**

Group Name	N	Missing	Mean	Std Dev	SEM
COA	9	0	136.522	21.007	7.002
CON	9	0	131.644	12.357	4.119
Difference	4.878				

t = 0.600 with 16 degrees of freedom. (P = 0.557)

Appendix K: Data and ANOVA tables – Blood pressure following exercise

K.1 Brachial systolic blood pressure – Leg exercise

	CoA		Control	
	PRE	**POST**	**PRE**	**POST**
1	116	130	124	129
2	99	103	103	103
3	120	122	102	95
4	120	131	101	97
5	102	116	107	115
6	103	99	109	123
7	115	133	95	100
8	109	129	110	116
9	108	122	104	117
Mean	**110**	**121**	**106**	**111**
SEM	3	4	3	4

ANOVA – Summary of all effects

Source of Variation	DF	SS	MS	F	P
GROUP	1	453.335	453.335	2.450	0.137
SUBJECT(GROUP)	16	2961.028	185.064		
TIME	1	511.891	511.891	18.229	<0.001
GROUP x TIME	1	75.835	75.835	2.701	0.120
Residual	16	449.306	28.082		
Total	35	4451.394	127.183		

K.2 Popliteal systolic blood pressure – Leg exercise

	CoA		Control	
	PRE	**POST**	**PRE**	**POST**
1	124	131	120	*125
2	98	113	112	113
3	105	107	96	99
4	129	130	101	103
5	116	132	118	121
6	119	122	124	135
7	124	132	98	108
8	104	113	115	123
9	106	120	124	131
Mean	**114**	**122**	**112**	**118**
SEM	4	3	4	4

ANOVA – Summary of all effects

Source of Variation	DF	SS	MS	F	P
GROUP	1	86.188	86.188	0.388	0.542
SUBJECT(GROUP)	16	3650.702	228.169		
TIME	1	439.002	439.002	35.667	<0.001
GROUP x TIME	1	17.787	17.787	1.445	0.248
Residual	15	184.623	12.308		
Total	34	4396.032	129.295		

**Missing value replaced with expected value*

K.3 Arm-Leg gradient – Leg exercise (mmHg)

	CoA		Control	
	PRE	**POST**	**PRE**	**POST**
1	-9	-1	5	4
2	2	-10	-10	-10
3	15	15	7	-4
4	-9	1	-1	-6
5	-14	-16	-12	-6
6	-16	-23	-15	-12
7	-9	1	-3	-8
8	5	16	-6	-7
9	2	2	-20	-14
Mean	**-3**	**-2**	**-6**	**-7**
SD	10	13	9	5

ANOVA – Summary of all effects

Source of Variation	DF	SS	MS	F	P
GROUP	1	136.435	136.435	0.845	0.372
SUBJECT(GROUP)	16	2583.897	161.494		
TIME	1	1.144	1.144	0.0488	0.828
GROUP x TIME	1	18.658	18.658	0.797	0.385
Residual	16	374.619	23.414		
Total	35	3114.752	88.993		

K.4 Brachial mean arterial pressure – Leg Exercise (mmHg)

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	83	80	83	78	84	89
2	69	67	64	68	71	65
3	91	86	82	73	62	63
4	83	82	75	66	60	62
5	70	64	66	77	78	70
6	63	62	66	75	56	61
7	78	73	75	64	64	67
8	78	83	83	75	79	74
9	79	75	76	75	75	76
Mean	**77**	**75**	**74**	**72**	**70**	**70**
SD	9	9	8	5	10	9

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	279.267	279.267	1.603	0.224
SUBJECT(GROUP)	16	2787.890	174.243		
TIME	2	80.726	40.363	2.516	0.097
GROUP x TIME	2	0.150	0.0751	0.00468	0.995
Residual	32	513.462	16.046		
Total	53	3661.495	69.085		

K.5 Brachial systolic blood pressure – Arm exercise

	CoA		Control	
	PRE	**POST**	**PRE**	**POST**
1	110	*116	114	113
2	105	116	106	111
3	117	126	92	99
4	116	123	99	101
5	107	116	105	110
6	97	95	108	123
7	115	119	102	107
8	113	116	106	125
9	106	115	106	109
Mean	**109**	**116**	**104**	**111**
SEM	2	3	2	3

Normality >0.05; Data transformed via natural logarithm:

	CoA		Control	
	PRE	**POST**	**PRE**	**POST**
1	4.70	4.75	4.74	4.73
2	4.65	4.75	4.66	4.71
3	4.76	4.84	4.52	4.60
4	4.75	4.81	4.59	4.62
5	4.67	4.75	4.65	4.70
6	4.57	4.55	4.68	4.81
7	4.74	4.78	4.62	4.67
8	4.72	4.75	4.66	4.83
9	4.66	4.74	4.66	4.69
Mean	**4.69**	**4.75**	**4.64**	**4.71**
SEM	0.02	0.03	0.02	0.03

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	0.0185	0.0185	2.137	0.163
SUBJECT(GROUP)	16	0.142	0.00890		
TIME	1	0.0303	0.0303	26.811	<0.001
GROUP x TIME	1	0.000123	0.000123	0.109	0.746
Residual	15	0.0170	0.00113		
Total	34	0.208	0.00613		

**outlier replaced with expected value*

K.6 Popliteal systolic blood pressure – Arm exercise

	CoA		Control	
	PRE	**POST**	**PRE**	**POST**
1	127	133	111	127
2	114	106	114	120
3	120	126	105	108
4	129	131	108	116
5	107	122	118	121
6	122	129	125	142
7	112	131	111	110
8	103	111	115	119
9	105	113	121	111
Mean	**115**	**122**	**114**	**119**
SEM	3	3	2	3

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	4.352	4.352	0.0282	0.869
SUBJECT(GROUP)	17	2619.911	154.112		
TIME	1	365.475	365.475	12.289	0.003
GROUP x TIME	1	9.264	9.264	0.312	0.584
Residual	17	505.578	29.740		
Total	37	3511.763	94.913		

K.7 Arm-Leg SBP gradient (mmHg) – Arm exercise

	CoA		Control	
	PRE	**POST**	**PRE**	**POST**
1	-18	31	3	-14
2	-9	10	-9	-9
3	-3	0	-14	-9
4	-14	-8	-10	-15
5	0	-6	-13	-11
6	-26	-34	-17	-19
7	4	-12	-9	-3
8	10	5	-9	6
9	1	2	-15	-2
Mean	**-6**	**-1**	**-10**	**-8**
SD	11	18	6	8

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
group	1	286.174	286.174	1.920	0.185
subject(group)	16	2384.944	149.059		
time	1	91.840	91.840	0.803	0.383
group x time	1	19.507	19.507	0.171	0.685
Residual	16	1829.278	114.330		
Total	35	4611.743	131.764		

K.8 Brachial mean arterial pressure (mmHg) – Arm exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	75	82	84	81	83	81
2	72	71	69	69	71	70
3	84	78	77	68	66	65
4	86	79	83	65	63	66
5	71	72	70	75	77	77
6	63	61	59	64	72	65
7	77	71	68	69	65	61
8	84	81	82	73	77	75
9	75	70	73	78	74	76
Mean	**76**	**74**	**74**	**71**	**72**	**71**
SD	7	7	8	6	7	7

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	160.296	160.296	1.232	0.283
SUBJECT(GROUP)	16	2081.439	130.090		
TIME	2	23.914	11.957	1.644	0.209
GROUP x TIME	2	21.245	10.622	1.460	0.247
Residual	32	232.752	7.274		
Total	53	2519.646	47.540		

Appendix L: Data and ANOVA Tables – Stiffness response to exercise

L.1 Carotid distensibility – leg exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	0.0095	0.0096	0.0082	0.0052	0.0067	0.0063
2	0.0091	0.0076	0.0089	0.0080	0.0084	0.0087
3	0.0089	0.0077	0.0105	0.0229	0.0122	0.0115
4	0.0083	0.0069	0.0101	0.0089	0.0069	0.0058
5	0.0154	0.0141	0.0131	0.0109	0.0091	0.0091
6	0.0112	0.0087	0.0105	0.0074	0.0105	0.0089
7	0.0110	0.0150	0.0129	0.0132	0.0147	0.0134
8	0.0062	0.0079	0.0081	0.0075	0.0057	0.0048
9	0.0085	0.0068	0.0071	0.0094	0.0111	0.0123
Mean	**0.0098**	**0.0094**	**0.0099**	**0.0104**	**0.0095**	**0.0090**
SEM	0.0009	0.0010	0.0007	0.0017	0.0010	0.0010

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	0.00000216	0.00000216	0.0729	0.791
SUBJECT(GROUP)	16	0.000478	0.0000298		
TIME	2	0.0000175	0.00000873	2.248	0.123
GROUP x TIME	2	0.0000000427	0.0000000214	0.00550	0.995
Residual	31	0.000120	0.00000389		
Total	52	0.000617	0.0000119		

L.2 Carotid distensibility – arm exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	0.0096	0.0065	0.0068	0.0092	0.0083	0.0090
2	0.0088	0.0075	0.0069	0.0081	*0.0068	0.0055
3	0.0095	0.0118	0.0095	0.0178	0.0153	0.0135
4	0.0075	0.0104	0.0070	0.0099	0.0129	0.0116
5	0.0129	0.0122	0.0135	0.0103	0.0097	0.0080
6	0.0079	0.0088	0.0093	0.0071	0.0059	0.0051
7	0.0087	0.0114	0.0098	0.0122	0.0084	0.0100
8	0.0056	0.0070	0.0080	0.0069	0.0051	0.0054
9	0.0084	0.0085	0.0070	0.0078	0.0100	0.0091
Mean	**0.0088**	**0.0094**	**0.0086**	**0.0099**	**0.0092**	**0.0086**
SEM	0.0007	0.0007	0.0007	0.0011	0.0011	0.0010

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	0.00000107	0.00000107	0.0582	0.812
SUBJECT(GROUP)	16	0.000296	0.0000185		
TIME	2	0.00000593	0.00000297	1.792	0.183
GROUP x TIME	2	0.00000489	0.00000245	1.477	0.244
Residual	31	0.0000513	0.00000166		
Total	52	0.000360	0.00000692		

** missing value replaced with expected value.*

L.3 Central pulse wave velocity – leg exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	3.2	3.1	3.0	2.7	2.9	2.7
2	-------	-------	-------	-------	-------	-------
3	2.8	2.7	2.6	2.2	2.3	2.2
4	2.4	2.3	2.2	2.2	2.2	2.1
5	2.6	2.7	2.6	3.4	3.3	3.2
6	2.7	2.6	2.4	2.3	2.6	2.4
7	3.1	2.9	2.9	2.2	2.3	2.3
8	2.8	2.4	2.3	2.5	2.6	2.5
9	2.2	2.2	2.1	2.8	2.7	2.6
Mean	**2.7**	**2.6**	**2.5**	**2.6**	**2.6**	**2.5**
SEM	0.1	0.1	0.1	0.1	0.1	0.1

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	0.0524	0.0524	0.151	0.703
SUBJECT(GROUP)	14	4.852	0.347		
TIME	2	0.103	0.0517	8.264	0.002
GROUP x TIME	2	0.0476	0.0238	3.810	0.034
Residual	28	0.175	0.00625		
Total	47	5.230	0.111		

L.4 Central pulse wave velocity – arm exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	3.0	3.1	3.0	2.6	3.1	3.0
2	-------	-------	-------	-------	-------	-------
3	2.6	2.5	2.5	2.1	2.4	2.3
4	2.3	3.3	2.6	2.2	2.3	2.2
5	2.6	2.6	2.5	3.2	3.2	3.0
6	2.5	2.6	2.6	2.4	2.7	2.6
7	3.0	3.1	2.9	2.3	2.3	2.2
8	2.5	3.1	3.1	2.5	2.6	2.5
9	2.7	2.6	2.6	2.6	2.7	2.5
Mean	**2.7**	**2.9**	**2.7**	**2.5**	**2.7**	**2.5**
SEM	0.1	0.1	0.1	0.1	0.1	0.1

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	0.0687	0.0687	2.186	0.161
SUBJECT(GROUP)	14	0.440	0.0314		
TIME	2	0.0495	0.0247	7.525	0.002
GROUP x TIME	2	0.000352	0.000176	0.0535	0.948
Residual	28	0.0921	0.00329		
Total	47	0.650	0.0138		

L.5 Non-exercised limb (upper limb) pulse wave velocity – leg exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	6.8	7.3	6.0	5.5	6.0	5.9
2	-------	-------	-------	-------	-------	-------
3	6.5	6.5	5.6	7.9	*8.4	9.2
4	6.1	7.7	7.0	6.5	7.0	6.9
5	5.5	5.0	4.9	5.8	6.2	6.3
6	6.6	5.6	5.9	6.5	6.7	6.6
7	5.5	5.5	5.3	6.2	6.5	6.9
8	5.6	5.3	5.9	6.2	6.1	6.1
9	5.2	5.5	5.6	8.3	7.1	8.2
Mean	**6.0**	**6.1**	**5.8**	**6.6**	**6.7**	**7.0**
SEM	0.2	0.4	0.2	0.3	0.3	0.4

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	0.207	0.207	4.907	0.044
SUBJECT(GROUP)	14	0.590	0.0422		
TIME	2	0.00167	0.000834	0.208	0.814
GROUP x TIME	2	0.0195	0.00975	2.429	0.106
Residual	28	0.112	0.00402		
Total	47	0.931	0.0198		

**outlier replaced with expected value*

L.6 Non-exercised limb (lower limb) pulse wave velocity – arm exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	6.6	7.2	7.2	4.9	5.4	4.9
2	-------	-------	-------	-------	-------	-------
3	7.4	7.2	7.8	8.0	6.7	6.4
4	11.0	6.8	5.3	7.6	8.2	7.4
5	4.8	5.7	5.9	6.4	5.9	6.7
6	6.8	6.8	6.4	6.1	5.8	6.0
7	7.0	5.7	6.4	6.8	6.5	7.6
8	8.5	6.1	5.8	6.9	8.2	7.8
9	6.2	7.2	6.8	8.5	8.4	8.5
Mean	**7.3**	**6.6**	**6.4**	**6.9**	**6.9**	**6.9**
SEM	0.7	0.2	0.3	0.4	0.4	0.4

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	0.562	0.562	0.153	0.701
SUBJECT(GROUP)	16	58.690	3.668		
TIME	2	3.276	1.638	1.628	0.212
GROUP x TIME	2	4.607	2.304	2.289	0.118
Residual	32	32.201	1.006		
Total	53	99.336	1.874		

L.7 Exercised limb (lower limb) pulse wave velocity – leg exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	7.4	6.7	6.2	5.0	5.7	6.3
2	-------	-------	-------	-------	-------	-------
3	4.6	4.8	4.2	6.3	5.8	6.1
4	10.8	11.6	11.2	7.4	5.2	5.4
5	5.1	5.3	5.3	7.7	6.6	6.9
6	6.8	8.1	7.0	6.6	5.1	5.7
7	7.2	6.8	6.2	5.2	5.7	5.8
8	6.8	10.7	11.5	7.1	7.8	7.9
9	9.6	8.8	9.3	7.1	8.1	10.3
Mean	**7.3**	**7.9**	**7.6**	**6.5**	**6.2**	**6.8**
SEM	0.7	0.9	1.0	0.4	0.4	0.6

Normality >0.05; Data transformed via natural logarithm:

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	1.92	1.99	1.80	1.71	1.79	1.77
2	-------	-------	-------	-------	-------	-------
3	1.88	1.87	1.72	2.07	2.12	2.22
4	1.81	2.05	1.95	1.88	1.94	1.93
5	1.71	1.61	1.60	1.76	1.82	1.84
6	1.88	1.72	1.78	1.88	1.91	1.88
7	1.70	1.71	1.67	1.83	1.87	1.94
8	1.73	1.68	1.77	1.82	1.81	1.82
9	1.65	1.71	1.72	2.11	1.96	2.10
Mean	**1.78**	**1.79**	**1.75**	**1.88**	**1.90**	**1.94**
SEM	0.04	0.06	0.04	0.05	0.04	0.05

ANOVA – Summary of all effects

GROUP	1	9.151	9.151	1.486	0.240
SUBJECT(GROUP)	16	98.523	6.158		
TIME	2	0.694	0.347	0.161	0.852
GROUP x TIME	2	2.424	1.212	0.564	0.574
Residual	32	68.761	2.149		
Total	53	179.553	3.388		

L.8 Exercised limb (upper limb) pulse wave velocity – arm exercise

	CoA			Control		
	PRE	**POST 5**	**POST 15**	**PRE**	**POST 5**	**POST 15**
1	6.1	6.3	5.9	5.7	6.1	5.6
2	-------	-------	-------	-------	-------	-------
3	6.8	6.0	6.7	8.0	6.6	7.9
4	6.9	5.0	6.5	7.5	7.4	8.0
5	5.9	5.4	5.2	6.9	6.5	7.1
6	6.6	6.0	6.3	7.5	5.5	5.2
7	5.9	5.6	6.1	6.3	5.0	5.6
8	6.0	5.2	5.0	5.7	6.2	6.5
9	5.5	5.7	5.6	8.1	7.0	7.2
Mean	**6.2**	**5.6**	**5.9**	**7.0**	**6.3**	**6.6**
SEM	0.2	0.2	0.2	0.3	0.3	0.4

ANOVA – Summary of all effects

Source of Variation	**DF**	**SS**	**MS**	**F**	**P**
GROUP	1	6.118	6.118	5.093	0.041
SUBJECT(GROUP)	14	16.817	1.201		
TIME	2	3.259	1.630	6.489	0.005
GROUP x TIME	2	0.0157	0.00786	0.0313	0.969
Residual	28	7.032	0.251		
Total	47	33.242	0.707		