Arterial Compliance and Distensibility: A Comparison of Three Measurement Sites

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Abstract

Objective: Prior research has shown that measures of arterial wall thickness and arterial elasticity have predictive and prognostic value in the formation of atherosclerosis. We sought to determine if these measures were consistent in various vascular beds throughout the arterial system.

Methods: We examined intima-media thickness (IMT), wall cross-sectional area (WCSA), lumen diameter (LD), cross-sectional (CSC1, CSC2) and diameter compliance (DC), cross-sectional (CSD) and diameter distensibility (DD), and incremental elastic modulus (IEM) in the common carotid artery, the brachial artery, and the abdominal aorta in children and adolescents ages 8.1 – 21.3 years old (n = 93 subjects; 45 males, 48 females). Spearman's correlation analysis was used to determine relationships between measurements from different arteries.

Results: LD was found to be associated (ρ = 0.282, P = 0.009) between the brachial and carotid arteries. Between the brachial artery and abdominal aorta, LD (ρ = 0.456, P < 0.001), CSD% (ρ = 0.230, P = 0.027), and IEM (ρ = 0.221, P = 0.037) showed a significant association. Between the carotid artery and abdominal aorta, LD (ρ = 0.334, P = 0.002), DD% (ρ = 0.317; P = 0.001), CSD% (ρ = 0.317, P = 0.002), CSC2 (ρ = 0.283, P = 0.006), and IEM (ρ = 0.312, P = 0.002) were found to be associated. IMT was not found to be associated between any measurement sites.

Conclusion: The carotid artery and abdominal aorta showed moderate correlation on most arterial elasticity measures. However, only a few brachial arterial elasticity measures showed a significant correlation with those in the carotid or abdominal arteries.

Finally, there was no correlation between IMT at the three different sites. It is possible that these findings are a result of the varying amounts of muscular versus elastic content of these three arteries. Future research should examine the relative prognostic value of each measurement site in predicting atherosclerosis and cardiovascular disease risk.

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List of Abbreviations

a-: abdominal aorta

b-: brachial artery

BP: blood pressure

c-: common carotid artery

CSC: cross-sectional compliance

CSD%: cross-sectional distensibility (percentage)

DBP: diastolic blood pressure

DC: diameter compliance

DD%: diameter distensibility (percentage)

IEM: incremental elastic modulus

IMT: intima-media thickness

LD: lumen diameter

ΔP: pulse pressure

SBP: systolic blood pressure

WCSA: wall cross-sectional area

CHAPTER 1. Introduction

Introduction

Cardiovascular disease is the leading cause of mortality worldwide (World Health Organization, 2014), and accounts for 23.5% of deaths in the United States (National Center for Health Statistics, 2014). Some pharmacotherapies and lifestyle interventions are available that slow or possibly even reverse the progression of atherosclerosis and associated risk factors (Jani & Rajkumar, 2006; Dengel & Bronas, 2010; Ross, 1993; Giannattasio, et al., 2001; Fernhall & Agiovlasitis, 2008), so early identification of increased risk or abnormalities is valuable. Several methods exist for early identification of at-risk individuals.

Changes in the structure and function of arteries are often associated with atherosclerosis, and are an early indicator of cardiovascular disease. Atherosclerotic calcification and plaque formation can cause increased arterial wall thickness and lead to decreased arterial elasticity (Jani & Rajkumar, 2006). Clinically increased arterial wall thickness in the carotid artery is commonly used as a marker of atherosclerosis (Chambless, et al., 1997; Jani & Rajkumar, 2006; Urbina, et al., 2006). Recently, arterial elasticity has been examined as a possible biomarker of atherosclerosis (van Popele, et al., 2001; McVeigh, et al., 1999) and cardiovascular disease (Marlatt, Kelly, Steinberger, & Dengel, 2013; Havlik, et al., 2003; Fjeldstad, Montgomery, & Gardner, 2008).

Arterial wall thickness and elasticity can be measured at multiple arterial locations. While many studies use the carotid artery as a measurement site (Dengel & Bronas, 2010), other studies have established the value of performing the measures in the abdominal aorta (Dawson, Sonka, Blecha, Lin, & Davis, 2009) and the brachial artery

(Urbina, Brinton, Elkasabany, & Berenson, 2002); however, the relationship between the measures across arterial beds has not been well-established. The present study sought to examine this relationship to determine whether measures of arterial elasticity were consistent across vessels in an individual. We hypothesized that arterial wall thickness and elasticity would be related across three measurement sites: carotid artery, brachial artery, and abdominal aorta.

The current state of the literature and the present study's methodology, findings, and conclusions will be discussed in the following chapters:

Chapter two summarizes the current state of the literature surrounding atherosclerosis pathophysiology and its relationship with arterial wall thickness and elasticity, the value of these measurements, measurement sites used in prior research, and a review of prior studies that have compared these measures across measurement sites.

Chapter three discusses the methodology of the present study, including information about the study population, measurement techniques and calculations, and statistical methods.

Chapter four describes the results of the present study by examining whether measurements are correlated the carotid artery, brachial artery, and abdominal aorta.

Chapter five discusses the significance of the findings, elaborates on limitations, and addresses future implications of the present study.

CHAPTER 2. Literature Review

Literature Review

Blood Vessel Structure

Endothelial cells line all blood vessels and are in direct contact with the blood that flows through the lumen (Marieb, Wilhelm, & Mallatt, 2014). This monolayer of endothelial cells is called the tunica intima, and it provides a smooth surface for blood to flow along with minimal friction. All blood vessels except capillaries have two additional layers: (a) the middle layer, called the tunica media, composed of smooth muscle cells and elastic fibers; and (b) the outermost layer, called the tunica adventitia, composed of connective tissue. The tunica media's smooth muscle cells wrap around the blood vessel rather than running longitudinally, and when these cells contract, they decrease the diameter of the blood vessel (i.e., vasoconstriction). When these smooth muscle cells relax, causing the blood vessel to increase in diameter (i.e., vasodilation). Vasoconstriction and vasodilation are a result of sympathetic nervous system stimulation and local factors. The elastic fibers in the tunica media provide elasticity and strength against the blood pressure changes that happen with each heartbeat. The tunica adventitia's connective tissue fibers run longitudinally along the blood vessels and provide strength, protection, and stability (Marieb, Wilhelm, & Mallatt, 2014).

Atherosclerosis: Pathophysiology and Disease Progression

In addition to their anatomical function, endothelial cells also serve important autocrine, paracrine, and endocrine functions (Dengel & Bronas, 2010; Pohl, Holtz, Busse, & Bassenge, 1986; Ross, 1993). Substances released from the endothelium affect

the smooth muscle cells to cause vasodilation or vasoconstriction, which helps regulate vascular tone and blood flow. These same substances inhibit many aspects of atherogenesis, including inhibiting platelet adhesion and aggregation, decreasing thrombogenicity, and inhibiting pathophysiological smooth muscle cell proliferation (Quyyumi, 1998; Corretti, et al., 2002; Dengel & Bronas, 2010; Ross, 1993).

Given the anti-atherogenic properties of some of the substances released by the endothelium, it is not surprising that endothelial dysfunction is thought to be an early sign of atherosclerosis (Dengel & Bronas, 2010; Corretti, et al., 2002; Quyyumi, 1998; Ross, 1993). The exact pathophysiology and causes of atherosclerosis are not fully understood, so it is uncertain if endothelial dysfunction is the first step of atherosclerosis or if another physiological change occurs first to cause the endothelial dysfunction.

Atherosclerosis is hypothesized to be a protective response to damage to the endothelium and smooth muscle cells in the arterial wall (Ross, 1993). First, likely because of injury to the arterial wall, a fatty streak consisting of lipid-rich macrophages and T lymphocytes forms below the endothelium. Then, as atherosclerosis progresses, these fatty streaks become intermediate lesions that consist of alternating layers of macrophages and smooth muscle cells. Finally, these lesions become fibrous plaques that may occlude the artery or may rupture, causing an embolism. Smooth muscle cells form a dense connective tissue matrix cap consisting of elastic fiber proteins, collagen, and proteoglycans. The cap covers lipids, macrophages, T lymphocytes, and necrotic debris from dead macrophages. Each stage of plaque formation becomes progressively larger, and it is common for the arterial injuries to have a chronic or episodic nature, so plaque

development tends to progress (Ross, 1993).

Early Identification of Atherosclerosis

While atherosclerosis and cardiovascular damage tend to accumulate over time, it is possible to slow or perhaps even reverse the disease process (Berenson, et al., 1998; Jani & Rajkumar, 2006; Ross, 1993). Because of the progressive state of the illness, it is important to identify cardiovascular impairment as early as possible in order to have the largest impact with an intervention. There are a variety of methods for identifying sub-clinical atherosclerosis by examining arterial structure and function, including non-invasive imaging of arterial wall structure and the arterial response to pressure changes (Fernhall & Agiovlasitis, 2008; Dengel & Bronas, 2010).

Intima-media thickness (IMT). The IMT is the combined width of the intima and media layers of an artery, measured as the space from the intima-media border to the media-adventitia border (Urbina, et al., 2006). Throughout the atherosclerotic process, the fatty streaks, intermediate lesions, and fibrous plaques in an affected artery progressively thicken the intimal layer and eventually decrease the lumen diameter. Some researchers believe that initial increases in IMT may be the result of an adaptive response in the medial layer to changes in lumen diameter, stress, and pressure, rather than local atherosclerotic damages in the intimal layer (Oren, Vos, Uiterwaal, Grobbee, & Bots, 2003; Bots, Hofman, & Grobbee, 1997).

IMT is commonly used as a clinical marker of generalized atherosclerosis and is

often used as an end-point in intervention studies for atherosclerosis (Chambless, et al., 1997; Jani & Rajkumar, 2006; Urbina, et al., 2006). An increase in IMT is associated with an increased risk of cardiovascular disease and cardiovascular events including myocardial infarction, stroke, and death (Salonen & Salonen, 1991; Bots, Hoes, Hofman, Witteman, & Grobbee, 1999; Bots, Hoes, Koudstaal, Hofman, & Grobbee, 1997; Hodis, et al., 1998; Chambless, et al., 1997; O'Leary, et al., 1999). In addition, increased carotid IMT is also associated with the presence or severity of other conditions, including familial hypercholesterolemia, hypertension, obesity, diabetes mellitus, metabolic syndrome, HIV, and Kawasaki disease (Urbina, et al., 2006).

IMT changes provide a signal to intervene. Early identification of at-risk individuals allows for earlier interventions, possibly allowing for more of a treatment effect. Interventions targeting IMT can be effective: certain pharmacotherapies and lifestyle interventions slow the progressive increase of IMT or even reverse it (Jani & Rajkumar, 2006; Dengel & Bronas, 2010; Dinenno, et al., 2001; Moreau, Silver, Dinenno, & Seals, 2006; Fernhall & Agiovlasitis, 2008), so early identification is valuable.

Arterial elasticity (compliance and distensibility). The larger, more elastic arteries in the body help absorb the pressure (and flow) variations that occur with each heartbeat, providing a more steady flow to the smaller vasculature (Jani & Rajkumar, 2006). During cardiac systole, the large arteries expand, accommodating much of the increased blood volume and pressure. At the start of diastole, the elastic recoil of the

large arteries push the blood through the coronary and peripheral vasculature.

Compliance and distensibility are common measures of arterial elasticity (Marlatt, Kelly, Steinberger, & Dengel, 2013). Arterial compliance is defined as the absolute change in arterial volume (ΔV) for a change in pressure ($\Delta V/\Delta P$) (Reneman, Meinders, & Hoeks, 2005), and is a marker of the artery's ability to store volume and buffer pressure changes that occur during the cardiac cycle. Arterial distensibility is commonly defined as the *relative* change in arterial volume ($\Delta V/V$) for a change in pressure ($\Delta V/V/\Delta P$), and is a marker of the mechanical load of the arterial wall. Both arterial compliance and distensibility can be estimated using the change in luminal cross-sectional area rather than volume; these are nearly identical as the arterial length changes are negligible (Reneman, Meinders, & Hoeks, 2005). Measuring an artery's response to the pressure changes throughout the cardiac cycle provides insight into the cardiovascular health of an individual.

When arterial elasticity decreases, systolic pressure and ventricular afterload increase, and this can eventually lead to the progression of atherosclerosis, left ventricular hypertrophy, and ventricular failure (Marchais, Guerin, Pannier, Delavaud, & London, 1993; Urbina, et al., 2006; Reneman, Meinders, & Hoeks, 2005). In a healthy cardiovascular system, the pressure waves from cardiac contractions return during diastole (Jani & Rajkumar, 2006). When arterial elasticity decreases, the pressure wave from a cardiac contraction occurs during systole, resulting in a disproportionate increase in systolic pressure. As a result, cardiac workload increases, and coronary blood flow during diastole decreases (Jani & Rajkumar, 2006), placing stress on the cardiovascular

system.

Atherosclerosis-associated calcification and plaque formation cause decreased arterial elasticity (Jani & Rajkumar, 2006; Oren, Vos, Uiterwaal, Grobbee, & Bots, 2003). Indeed, decreased arterial elasticity is associated with cardiovascular disease and adverse cardiovascular outcomes (Marlatt, Kelly, Steinberger, & Dengel, 2013; Havlik, et al., 2003; Fjeldstad, Montgomery, & Gardner, 2008; van Popele, et al., 2001; McVeigh, et al., 1999; Blacher, Asmar, Djane, London, & Safar, 1999; Cruickshank, et al., 2002; Laurent, et al., 2001). In children, decreased arterial distensibility is associated with hyperinsulinemia (Urbina, Bean, Daniels, D'Alessio, & Dolan, 2007), increased blood pressure (Whincup, et al., 2005), type 1 diabetes mellitus (Parikh, et al., 2000), a family history of myocardial infarction (Riley, et al., 1986), obesity (Aggoun, et al., 2000), and elevated levels of cholesterol (Leeson, et al., 2000) and leptin (Singhal, et al., 2002).

Effective interventions are available. Lifestyle modification and certain pharmacotherapies can improve arterial elasticity (Giannattasio, et al., 2001; Tanaka, et al., 2000; Jani & Rajkumar, 2006; Fernhall & Agiovlasitis, 2008). Early interventions can have a greater treatment effect (Fernhall & Agiovlasitis, 2008), so early identification of abnormalities is valuable.

Measurement sites. Coronary and peripheral vascular health have been shown to be closely related (Anderson, et al., 1995), so tests examining the peripheral arteries may provide insight into the health of the full cardiovascular system. Increased carotid IMT is associated with atherosclerosis in other arterial beds (Burke, et al., 1995; Allan,

Mowbray, Lee, & Fowkes, 1997; O'Leary, et al., 1999), and arterial compliance is similar across measurement sites in the elderly (Laogun & Gosling, 1982). However, given the local nature of the arterial wall's thickening response to atherosclerotic processes, and the varying composition of the arterial wall depending on the relative distance from the heart to the periphery, different arteries may have differing IMT, compliance, and distensibility measures, especially in younger individuals without clinical cardiovascular disease.

IMT. IMT has been measured in multiple arterial beds, including the carotid (Allan, Mowbray, Lee, & Fowkes, 1997; Bots, Hofman, & Grobbee, 1997; Salonen & Salonen, 1991; Chambless, et al., 1997; O'Leary, et al., 1999; Halcox, et al., 2009; Riley, Evans, Sharrett, Burke, & Barnes, 1997), abdominal aorta (Dawson, Sonka, Blecha, Lin, & Davis, 2009), and femoral (Moreau, Silver, Dinenno, & Seals, 2006; Dinenno, et al., 2001) arteries. While the carotid artery is the preferred site of IMT measurements (Allan, Mowbray, Lee, & Fowkes, 1997), other locations may provide additional information or respond to interventions differently (Dengel, et al., 2014; Dinenno, et al., 2001; Moreau, Silver, Dinenno, & Seals, 2006; van der Meer, et al., 2004). One study examined the relationship of cardiovascular risk factors with aortic and carotid IMT in youth (Dawson, Sonka, Blecha, Lin, & Davis, 2009). The researchers found that while both measurement sites were associated with cardiovascular risk factors, the aortic IMT was more strongly associated with most risk factors. This possibly indicates a stronger, earlier marker of atherosclerosis, and is supported by research showing that atherosclerotic lesions occur in the aorta in younger ages than in the coronary and carotid arteries (Dawson, Sonka, Blecha, Lin, & Davis, 2009). Another study had similar findings: children with

hypercholesterolemia and diabetes had increased aortic and carotid IMT compared to healthy controls, but aortic IMT showed a greater increase over controls than carotid IMT did (Järvisalo, et al., 2001). Interestingly, these studies also tended to show a stronger association between the aortic IMT and metabolic syndrome risk factors (i.e. abdominal obesity, high triglycerides, and low high-density lipoprotein cholesterol), but carotid IMT showed a stronger association with total cholesterol and low-density lipoprotein cholesterol (Dawson, Sonka, Blecha, Lin, & Davis, 2009).

It is possible that different arteries in the body reflect different stages of atherosclerosis, and that certain sites provide more differential information in a certain age group or population than in other populations. In support of this, measures of subclinical atherosclerosis in multiple sites indicates an increased risk for atherosclerosis, so it is possible that different sites provide complementary information into an individual's risk (Dawson, Sonka, Blecha, Lin, & Davis, 2009).

Arterial elasticity. Arterial elasticity has been measured in many arterial beds, including the carotid (Liao, Riley, Chambless, Szklo, & Heiss, 1999; Tounian, et al., 2001), femoral (Benetos, Laurent, Hoeks, Boutouyrie, & Safar, 1993; Laogun & Gosling, 1982), abdominal aorta (Oren, Vos, Uiterwaal, Grobbee, & Bots, 2003; Sonesson, Hansen, Stale, & Länne, 1993), brachial (Urbina, Bean, Daniels, D'Alessio, & Dolan, 2007; Boutouyrie, et al., 1992; Whincup, et al., 2005), radial (Boutouyrie, et al., 1992), and subclavian (Laogun & Gosling, 1982) arteries. In general, the carotid artery and abdominal aorta are very common measurement sites, whereas more peripheral, less elastic arteries such as the brachial artery are less commonly measured (Fernhall &

Agiovlasitis, 2008). However, these peripheral arteries do show varying elasticity with changing disease states (Whincup, et al., 2005), so they may still add value.

The Relationship Between Measurement Sites

The exact relationship between measures of arterial wall thickness and arterial elasticity across different arterial beds—in particular, the carotid artery, brachial artery, and abdominal aorta—has been studied very little. Researchers have examined how the different sites change in response to age or disease (Benetos, Laurent, Hoeks, Boutouyrie, & Safar, 1993; Boutouyrie, et al., 1992), but have not examined how the sites relate to each other. It is unclear whether the studies using different measurement sites can be compared, or if the findings from those studies would have been different if the researchers had used a different measurement site.

Using different methods than the present study, a partial correlation of R=0.35 (*p*-value not reported) was found between aortic and carotid IMT values in a study of 11- to 34-year-olds (Dawson, Sonka, Blecha, Lin, & Davis, 2009), but the researchers did not examine arterial elasticity or brachial measurements.

Marlatt et al. (2013), using the same methods as the present study, examined arterial elasticity in the brachial and carotid arteries in children and adults. They found significant correlations in distensibility and compliance across measurement sites in youth, but not adults.

Present Study

The present study examined the relationship between arterial structural and elasticity across three measurement sites: the left carotid artery, the abdominal aorta, and the left brachial artery. To our knowledge, prior research has not compared these three sites. It is important to determine if arterial structure and function are uniform throughout the vascular system. If this is confirmed in the present study, findings would suggest that comparisons across studies using different measurement sites might be valid and provide support for the use of alternative measurement sites when an individual has a condition that prohibits the preferred measurement site.

CHAPTER 3. Methodology

Methodology

The procedures followed in the present study adhered to the University of Minnesota's IRB and Health Insurance Portability and Accountability Act (HIPAA) guidelines. The study protocols were reviewed and approved by the University of Minnesota Institutional Review Board (IRB). All subjects and parents of underage subjects provided informed consent. Underage subjects provided informed assent.

Study Population

While overt cardiovascular disease is rare in youth, children and adolescents are not exempt from the precursor pathology (Berenson, et al., 1998; Urbina, et al., 2006). Therefore, the current study population includes youth. Subjects were between 8-22 years of age and were recruited from a population study examining endothelial health in children and adolescents with varying degrees of adiposity. Individuals were excluded from the study if they had illnesses or took medication that was known to affect endothelial health or cardiovascular function. A total of 93 subjects (48 females, 45 males) had arterial elasticity vascular data for all three measurement sites measured during a single visit.

Measurements

Standing height was measured to the nearest millimeter, weight was measured using a Scale-Tronix 5002 digital scale, and blood pressure was measured using an automated sphygmomanometer (Model BP-8800C; Colin Press-Mate, San Antonio, TX,

USA) on the right arm. Body mass index (BMI; kg/m^2) was calculated as weight (kg) divided by height (m^2). BMI percentile was calculated using the 2000 CDC Growth Charts for the United States (Kuczmarski, et al., 2002).

Vascular testing. All vascular testing was performed in a quiet, temperature-controlled environment (22-23°C) in the University of Minnesota Clinical and Translational Science Institute and in the University of Minnesota General Clinical Research Center after participants had been fasting for 10 hours. Subjects were asked to avoid medication and caffeine prior to the study. Three highly trained laboratory technicians collected and analyzed the data.

Subjects rested for 15 minutes in the supine position. A standard ultrasound (Acuson, Sequoia 512, Siemens Medical Solutions USA, Inc. Mountain View, CA; carotid and brachial: 15L8 MHz linear array probe; abdominal: 9L4 transducer) was used to obtain B-mode images of the carotid, brachial, and abdominal arteries along the long axes. The transducer was held at a constant distance from the skin and at a fixed point over the imaged artery.

All images were saved for later analysis, and an electronic an electronic wall-tracking software program (Vascular Research Tools 5, Medical Imaging Applications, LLC, Iowa City, IA) was be used for the analysis of arterial lumen diameters, IMT, and elasticity as previously described (Dengel, et al., 2014). An electrocardiogram determined end-diastolic timing of the images (gated by R waves).

Arterial elasticity calculations. A variety of calculations were performed on the

collected data (Medical Imaging Applications, LLC, 2006).

Pulse pressure (ΔP; mmHg) was calculated as:

$$\Delta P = Systolic\ Pressure\ (SBP) - Diastolic\ Pressure(DBP)$$

Diameter distensibility percentage (DD%; %) was calculated as:

$$DD\% = \frac{D_{max} - D_{min}}{D_{min}} \times 100\%$$

Cross-sectional distensibility percentage (CSD%; %) was calculated as:

$$CSD\% = \frac{\pi(0.5\ D_{max})^2 - \pi(0.5\ D_{min})^2}{\pi\ (0.5\ D_{min})^2} \times 100\% = \left(\frac{{D_{max}}^2 - {D_{min}}^2}{{D_{min}}^2}\right) \times 100\%$$

Diameter compliance (DC; mm/mmHg) was calculated as:

$$DC = \frac{D_{max} - D_{min}}{\Delta P}$$

Cross-sectional compliance one (CSC1; mm^2/mmHg) was calculated as:

$$CSC1 = \frac{\pi(0.5\ D_{max})^2 - \pi(0.5\ D_{min})^2}{\Delta P} = \frac{\pi({D_{max}}^2 - {D_{min}}^2)}{4\ \Delta P}$$

Cross-sectional compliance two (CSC2; 1/mmHg) was calculated as:

$$CSC2 = \frac{\pi(0.5\ D_{max})^2 - \pi(0.5\ D_{min})^2}{\pi(0.5\ D_{min})^2 \times \Delta P} = \frac{\left(\frac{{D_{max}}^2 - {D_{min}}^2}{{D_{min}}^2}\right)}{\Delta P} = \frac{CSD}{\Delta P}$$

Incremental elastic modulus (IEM; mmHg) was calculated as:

$$IEM = \frac{3\left\{1 + \left[\frac{\pi(0.5\ D_{max})^2}{\pi(0.5\ D_{min})^2}\right]\right\}}{CSC2} = \frac{3\left(1 + \frac{{D_{max}}^2}{{D_{min}}^2}\right)}{CSC2} = \frac{3\Delta P\left(1 + \frac{{D_{max}}^2}{{D_{min}}^2}\right)}{CSD}$$

Statistical Analysis

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical

analyses. Results are expressed as mean ± standard deviation (SD). An independent sample t-test was used to compare demographic characteristics. Spearman's correlation analysis (ρ) was used to evaluate the relationship between vascular measurements at the three site combinations: carotid and brachial, carotid and abdominal, and brachial and abdominal. An alpha value of 0.05 was denoted as statistically significant.

CHAPTER 4. Results

Results

Demographic Data

Demographic characteristics are shown in Table 1. There were no significant differences in age, height, weight, BMI, gender, or race between males and females.

Vascular Measurements

Mean left common carotid artery (c-) measurements are shown in Table 2. There were no significant differences between genders for measures of blood pressure (i.e. SBP, DBP, and ΔP). Similarly, measures of carotid arterial thickness (i.e. cIMT, cLD, cIMT/cLD, and cWCSA) and elasticity (i.e. cDD%, cCSD%, cDC, cCSC1, cCSC2, and cIEM) were not significantly different between genders.

Mean brachial artery (b-) measurement data are shown in Table 3. bLD and bCSC1 were significantly different between males and females. Measures of blood pressure (i.e. SBP, DBP, and ΔP), the remaining measures of brachial artery thickness (i.e. bIMT, bIMT/bLD, and bWCSA), and the remaining measures of brachial artery elasticity (i.e. bDD%, bCSD%, bDC, bCSC2, and bIEM) were not significantly different between genders.

Mean abdominal aorta (a-) measurement data are shown in Table 4. There were no significant differences between males and females for measures of blood pressure (i.e. SBP, DBP, and ΔP), abdominal aorta thickness (i.e. aIMT, aLD, aIMT/aLD, and aWCSA), or abdominal aorta elasticity (i.e. aDD%, aCSD%, aDC, aCSC1, aCSC2, or aIEM).

Spearman Correlations Between the Carotid and Brachial Arteries

The correlations between measurements at the carotid and brachial arteries are shown in Table 5. LD was correlated between these measurement sites; however, the remaining measures of arterial thickness (i.e. IMT, IMT/LD, and WCSA) were not significantly correlated. Additionally, measures of arterial elasticity (i.e. DD%, CSD%, DC, CSC1, CSC2, and IEM) were not significantly correlated.

When analyzed by gender, males showed significant correlations between these arteries for LD and WCSA, but not for other measures of arterial thickness (i.e. IMT and IMT/LD) or arterial elasticity (i.e. DD%, CSD%, DC, CSC1, CSC2, and IEM). Females did not show any significant correlations between these arteries for any measures of arterial thickness (i.e. IMT, LD, IMT/LD, and WCSA) or arterial elasticity (i.e. DD%, CSD%, DC, CSC1, CSC2, and IEM).

Spearman Correlations Between the Carotid Artery and Abdominal Aorta

The correlations between measurements at the carotid artery and abdominal aorta are shown in Table 6. LD was found to correlate between these measurement sites, even when divided by gender. DD% (Figure 1), CSD% (Figure 2), CSC2 (Figure 3), and IEM (Figure 4) were found to correlate between these measurement sites when both genders were combined (Figures 1-4, panel A); when divided by gender, these measurements were correlated for females (Figures 1-4, panel B) but not males (Figures 1-4, panel C). The remaining measures of arterial thickness and elasticity (i.e. IMT, IMT/LD, WCSA,

DC, and CSC1) were not correlated between measurement sites, even when divided by gender.

Spearman Correlations Between Abdominal Aorta and the Brachial Artery

The correlations between measurements at the brachial artery and the abdominal aorta are shown in Table 7. LD was found to correlate between measurement sites, even when divided by gender. CSD% and IEM were found to correlate between measurement sites, but not when divided by gender. WCSA was found to correlate between measurement sites for females only. The other arterial thickness and elasticity measures (i.e. IMT, IMT/LD, DD%, DC, CSC1, and CSC2) were not correlated between measurement sites, even when divided by gender.

CHAPTER 5. Discussion and Implications

Discussion and Implications

Summary of Findings

The carotid artery and abdominal aorta measurements were mild to moderately correlated for most arterial elasticity measures, except DC and CSC1. Because both of these are elastic arteries (Reneman, Meinders, & Hoeks, 2005), these results are not surprising. Additionally, in adults, carotid elasticity decreases with age, with the change in CSC2 more marked than CSC1 because the concurrent increase in LD counteracts increases in CSC1 (Reneman, Van Merode, Hick, Muytjens, & Hoeks, 1986). The increased LD is considered an adaptive response to the increase in CSC1 since it helps to prevent a reduction in the volume of blood that the arteries, ultimately preventing the blood pressure from rising too much (Reneman, Meinders, & Hoeks, 2005). It is possible that the lack of correlation for CSC1 is because the subjects were not diseased enough to begin to show differentiation in CSC1 measurements.

The brachial artery elasticity measurements were not correlated with the carotid artery elasticity measurements, and were only mildly correlated with the abdominal aorta elasticity measurements for CSD% and IEM. The finding that the brachial artery measurements are not correlated with the abdominal and carotid arteries is also not surprising. While the central arteries are highly elastic and have decreased influence from smooth muscle tone, the elasticity decreases toward the peripheral vessels as the elastin-to-collagen ratio in the wall decreases and smooth muscle bulk and tone becomes increasingly important in determining the compliance and distensibility of the vessel (Bank, et al., 1996; Bank, Kaiser, Rajala, & Cheng, 1999). Additionally, atherosclerosis

presents and progresses differently in different arteries, possibly due to differences in smooth muscle cell differences among the arteries (Ross, 1993). It is possible that some arteries are affected later in the disease progression and that the population examined in the current study was too young to be showing symptoms of atherosclerosis; a population with more progressive atherosclerosis may have different results. Finally, research has shown that aging and hypertension have differing effects on compliance and distensibility in different sites (Reneman, Meinders, & Hoeks, 2005). Aging appears to reduce distensibility in the common femoral artery but not in the deep and superficial femoral arteries, even though all three of these are considered muscular arteries. In addition, distensibility can vary by region of the artery; the common carotid artery is less affected by age than the carotid bulb. In hypertension, both compliance and distensibility are affected in the carotid artery but not the radial artery (Reneman, Meinders, & Hoeks, 2005). Other studies examining the relationship of each of the sites to aging, gender, and hypertension showed significant findings in the carotid artery and abdominal aorta, but not the brachial artery (Boutouyrie, et al., 1992). Further research is needed to see if the brachial and carotid artery measures correlate in older or more diseased populations.

The present study's findings are in contrast to prior research that found significant moderate correlations between brachial and carotid arterial elasticity measures (DD%, CSD%, DC, and CSC1) in youth (Marlatt, Kelly, Steinberger, & Dengel, 2013). The prior study had a much smaller sample size (n=39; 17 females and 22 males), and were a subset of a sample with a younger mean age (10.9 years). It is possible that the difference in findings was a result of age; aging has a different effect on vessel dynamics

in different arteries, particularly when comparing elastic versus muscular arteries (Reneman, Meinders, & Hoeks, 2005; Boutouyrie, et al., 1992). In support of this, the prior study did not show a correlation across these measures in older subjects (18-49 years) (Marlatt, Kelly, Steinberger, & Dengel, 2013). It is also possible that the different findings were a result of a difference in statistical methods: the prior study used a Pearson's correlation rather than a Spearman's correlation like the present study. A Pearson's correlation is less robust to outliers, particularly in a small sample size. The present study used a Spearman's correlation in order to account for the possibility of a monotonic relationship between sites. Further research is needed to examine the relationship across arterial beds in younger children.

LD was mild to moderately correlated across all measurement sites except in females when comparing the carotid and brachial arteries, but IMT and IMT/LD were not correlated across any measurement sites, and WCSA was only correlated between the brachial and abdominal aorta in females and between the carotid and brachial arteries in males. It is possible that this population was too healthy to have substantial changes in subjects' IMT; some research suggests that IMT changes may occur later in the atherosclerotic process (Koivistoinen, et al., 2012; Oren, Vos, Uiterwaal, Grobbee, & Bots, 2003). Early atherosclerotic formations (e.g. fatty streaks) do not change the IMT as much as late atherosclerotic formations (e.g. fibrous plaques) (Ross, 1993), and it is possible that these early-stage changes are too small to provide detectable differences in a young, healthy population like this.

Limitations of the Present Study

The present study used pressures measured in the brachial artery for the carotid artery and abdominal aorta pressures. While indirectly-measured brachial artery pressures have been shown to be good approximations of the pressures in other arteries in middle-aged adults suspected of cardiac illnesses and compared the brachial and ascending aorta (Borow & Newburger, 1982), this may not generalize to the current study population. Additionally, the pulsatile component of blood pressure varies dramatically from different portions of the vascular system, and the carotid, brachial, and femoral arteries were found to have varying pulse pressures (Benetos, Laurent, Hoeks, Boutouyrie, & Safar, 1993). In elastic arteries like the aorta and carotid arteries, the relationship between cross-sectional area and pressure is linear, but this is not true in more muscular arteries like the brachial and femoral arteries (Reneman, Meinders, & Hoeks, 2005). It is possible that the results would have been different if the pressures had been measured locally, rather than using the brachial artery to measure pressure.

The present study population consisted of primarily young, healthy subjects, and greater changes in arterial elasticity and arterial wall thickness that result in greater population differentiation are seen in adults (Marlatt, Kelly, Steinberger, & Dengel, 2013; Urbina, et al., 2006; Laogun & Gosling, 1982; Sonesson, Hansen, Stale, & Länne, 1993; Sass, et al., 1998; Ishizu, et al., 2004; Jourdan, et al., 2005). It is possible that an older or more diseased population would have had different findings.

Arterial elasticity responds differently in different arteries to changes in age and hypertension status (Reneman, Meinders, & Hoeks, 2005). This may mean that certain

measures may not correlate well in this population, but an older population may have better correlation. Additionally, given these varying responses, it is important to identify which arteries provide the earliest and most reliable predictive value; this research has not been conducted.

Conclusion

Arterial wall thickness is not correlated across different arterial beds in young healthy individuals. Most arterial elasticity measures are correlated between the abdominal aorta and carotid artery, whereas the brachial artery only has some moderate correlations with the abdominal aorta. Future research is needed to establish if these findings also apply to different populations, particularly older or more diseased populations.

Table 1. Demographic Data

Variable	Both	± SD	Female	± SD	Male	± SD	*P*-value
Age (years)	13.5	± 2.6	13.2	± 3.1	13.8	± 2.1	0.300
Height (cm)[a]	161.5	± 10.0	161.4	± 7.9	161.5	± 12.3	0.968
Weight (kg)[a]	70.0	± 23.0	75.5	± 24.1	63.5	± 20.6	0.137
BMI (kg/m^2)[a]	26.6	± 7.5	28.8	± 8.0	23.9	± 6.2	0.066
BMI Percentile	77.3	± 30.0	83.3	± 27.1	70.1	± 32.7	0.213
Gender (n, %)	93	100%	48	51.61%	45	48.39%	
Race (n, %)							0.745
Caucasian	62	66.67%	31	33.33%	31	33.33%	
African American	5	5.38%	2	2.15%	3	3.23%	
Asian	2	2.15%	1	1.08%	1	1.08%	
Hispanic	4	4.30%	2	2.15%	2	2.15%	
Other	5	5.38%	4	4.30%	1	1.08%	
Not reported	15	16.13%	8	8.60%	7	7.53%	

Abbreviations: SD, standard deviation; BMI, body mass index.

[a]Height, weight, BMI, and BMI percentile were only available for 33 subjects (18 females, 15 males).

Table 2. Mean (± SD) Left Carotid Measurements

Left Carotid Artery	Both	± SD	Female	± SD	Male	± SD	*P-value*
SBP (mmHg)	114	± 12	114	± 13	114	± 11	0.986
DBP (mmHg)	58	± 9	59	± 8	56	± 10	0.145
ΔP (mmHg)	57	± 9	55	± 9	58	± 10	0.167
cIMT (mm)	0.48	± 0.09	0.48	± 0.09	0.49	± 0.08	0.322
cLD (mm)	5.92	± 0.65	5.93	± 0.63	5.92	± 0.69	0.959
cIMT/cLD	0.08	± 0.02	0.08	± 0.02	0.08	± 0.02	0.482
cWCSA (mm2)	9.81	± 1.99	9.59	± 2.07	10.05	± 1.89	0.269
cDD%	13.72	± 3.01	13.77	± 3.42	13.67	± 2.54	0.880
cCSD%	29.45	± 6.87	29.58	± 7.80	29.31	± 5.80	0.850
cDC (mm/mmHg)	0.01416	± 0.00338	0.01432	± 0.00360	0.01400	± 0.00316	0.652
cCSC1 (mm2/mmHg)	0.13827	± 0.03703	0.13850	± 0.03744	0.13801	± 0.03701	0.950
cCSC2 (1/mmHg)	0.00525	± 0.00153	0.00533	± 0.00181	0.00516	± 0.00119	0.596
cIEM (mmHg)	1110.68	± 359.76	1110.94	± 400.35	1110.41	± 315.29	0.994

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; ΔP, pulse pressure; c-, carotid artery; IMT, intima-media thickness; LD, lumen diameter; WCSA, wall cross-sectional area; DD%, diameter distensibility (percentage); CSD%, cross-sectional distensibility (percentage); DC, diameter compliance; CSC, cross-sectional compliance; DD, diameter distensibility; IEM, incremental elastic modulus.

Table 3. Mean (± SD) Brachial Artery Measurements

Brachial Artery	Both	± SD	Female	± SD	Male	± SD	*P*-value
SBP (mmHg)	116	± 12	116	± 12	116	± 12	0.717
DBP (mmHg)	58	± 9	59	± 7	57	± 10	0.452
ΔP (mmHg)	58	± 9	58	± 10	58	± 9	0.804
bIMT (mm)[a]	0.14	± 0.09	0.12	± 0.05	0.17	± 0.12	0.133
bLD (mm)[b]	3.07	± 0.47	2.92	± 0.35	3.25	± 0.54	0.002*
bIMT/bLD[a]	0.05	± 0.03	0.04	± 0.02	0.05	± 0.03	0.283
bWCSA (mm^2)[a]	1.52	± 1.15	1.20	± 0.53	1.90	± 1.55	0.103
bDD%	3.71	± 1.56	3.71	± 1.68	3.71	± 1.45	0.979
bCSD%	7.59	± 3.28	7.60	± 3.52	7.58	± 3.03	0.970
bDC (mm/mmHg)	0.00213	± 0.00085	0.00205	± 0.00087	0.00222	± 0.00083	0.341
bCSC1 (mm^2/mmHg)	0.01150	± 0.00505	0.01045	± 0.00436	0.01263	± 0.00552	0.037*
bCSC2 (1/mmHg)	0.00146	± 0.00111	0.00143	± 0.00083	0.00150	± 0.00135	0.765
bIEM (mmHg)[c]	4995.63	± 2145.14	5171.52	± 2318.12	4811.74	± 1957.80	0.430

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; ΔP, pulse pressure; b-, brachial artery; IMT, intima-media thickness; LD, lumen diameter; WCSA, wall cross-sectional area; DD%, diameter distensibility (percentage); CSD%, cross-sectional distensibility (percentage); DC, diameter compliance; CSC, cross-sectional compliance; DD, diameter distensibility; IEM, incremental elastic modulus.

[a]IMT, IMT/LD, and WCSA measurements were only available for 35 subjects (19 females, 16 males).

[b]LD measurements were only available for 86 subjects (47 females, 39 males).

[c]IEM measurements were only available for 90 subjects (46 females, 44 males).

*Denotes statistical significance at $\alpha = 0.05$.

Table 4. Mean (± SD) Abdominal Aorta Measurements

Abdominal Aorta	Both	± SD	Female	± SD	Male	± SD	*P*-value
SBP (mmHg)	115	± 12	115	± 12	115	± 12	0.919
DBP (mmHg)	58	± 9	59	± 8	56	± 9	0.099
ΔP (mmHg)	57	± 10	55	± 9	59	± 11	0.114
aIMT (mm)[a]	0.48	± 0.17	0.46	± 0.15	0.51	± 0.20	0.549
aLD (mm)[b]	9.87	± 2.12	9.62	± 1.71	10.16	± 2.49	0.261
aIMT/cLD[a]	0.07	± 0.07	0.08	± 0.10	0.05	± 0.02	0.370
aWCSA (mm^2)[a]	22.21	± 32.98	26.62	± 44.52	16.99	± 8.20	0.458
aDD%	14.81	± 4.99	14.76	± 5.17	14.87	± 4.84	0.920
aCSD%	32.43	± 11.71	32.60	± 12.27	32.24	± 11.21	0.884
aDC (mm/mmHg)	0.0253	± 0.0100	0.0251	± 0.0098	0.0255	± 0.0104	0.847
aCSC1 (mm^2/mmHg)	0.4344	± 0.2114	0.4152	± 0.1795	0.4548	± 0.2413	0.374
aCSC2 (1/mmHg)	0.0059	± 0.0024	0.0060	± 0.0025	0.0058	± 0.0023	0.569
aIEM (mmHg)[c]	1106.16	± 598.39	1069.24	± 501.81	1144.76	± 688.92	0.555

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; ΔP, pulse pressure; a-, abdominal aorta; IMT, intima-media thickness; LD, lumen diameter; WCSA, wall cross-sectional area; DD%, diameter distensibility (percentage); CSD%, cross-sectional distensibility (percentage); DC, diameter compliance; CSC, cross-sectional compliance; DD, diameter distensibility; IEM, incremental elastic modulus.

[a]IMT, IMT/LD, and WCSA measurements were only available for 24 subjects (13 females, 11 males).

[b]LD measurements were only available for 82 subjects (44 females, 38 males).

[c]IEM measurements were only available for 90 subjects (46 females, 44 males).

Table 5. Spearman Correlations Between Carotid and Brachial Arteries

Gender	Both		Female		Male	
Variable	**Rho**	**(*P-value*)**	**Rho**	**(*P-value*)**	**Rho**	**(*P-value*)**
IMT (mm)[a]	0.202	(0.244)	0.118	(0.631)	0.424	(0.102)
LD (mm)[b]	0.282	(0.009)*	0.118	(0.431)	0.444	(0.005)*
IMT/LDa	0.198	(0.253)	0.156	(0.523)	0.239	(0.373)
WCSA (mm2)[a]	0.226	(0.192)	0.166	(0.497)	0.502	(0.048)*
DD%	0.012	(0.909)	0.097	(0.510)	-0.141	(0.357)
CSD%	0.010	(0.921)	0.101	(0.495)	-0.144	(0.345)
DC (mm/mmHg)	0.023	(0.828)	0.123	(0.406)	-0.056	(0.713)
CSC1 (mm2/mmHg)	0.027	(0.797)	0.074	(0.618)	0.001	(0.996)
CSC2 (1/mmHg)	0.069	(0.513)	0.079	(0.592)	0.026	(0.865)
IEM (mmHg)[c]	0.111	(0.296)	0.181	(0.229)	0.039	(0.804)

Abbreviations: SD, standard deviation; IMT, intima-media thickness; LD, lumen diameter; WCSA, wall cross-sectional area; DD%, diameter distensibility (percentage); CSD%, cross-sectional distensibility (percentage); DC, diameter compliance; CSC, cross-sectional compliance; DD, diameter distensibility; IEM, incremental elastic modulus.

[a]IMT, IMT/LD, and WCSA measurements were only available for 35 subjects (19 females, 16 males).

[b]LD measurements were only available for 86 subjects (47 females, 39 males).

[c]IEM measurements were only available for 90 subjects (46 females, 44 males).

*Denotes statistical significance at $\alpha = 0.05$.

Table 6. Spearman Correlations Between Carotid Artery and Abdominal Aorta

Gender	Both		Female		Male	
Variable	**Rho**	**(*P*-value)**	**Rho**	**(*P*-value)**	**Rho**	**(*P*-value)**
IMT (mm)[a]	0.109	(0.612)	0.330	(0.271)	-0.023	(0.947)
LD (mm)[b]	0.334	(0.002)*	0.303	(0.045)*	0.380	(0.019)*
IMT/LD[a]	0.004	(0.986)	0.033	(0.915)	0.210	(0.536)
WCSA (mm^2)[a]	0.037	(0.862)	0.335	(0.263)	-0.245	(0.467)
DD%	0.331	(0.001)*	0.346	(0.016)*	0.293	(0.051)
CSD%	0.317	(0.002)*	0.321	(0.026)*	0.284	(0.058)
DC (mm/mmHg)	0.102	(0.331)	0.043	(0.771)	0.171	(0.261)
CSC1 (mm^2/mmHg)	0.066	(0.530)	0.011	(0.943)	0.140	(0.361)
CSC2 (1/mmHg)	0.283	(0.006)*	0.339	(0.019)*	0.220	(0.147)
IEM (mmHg)[c]	0.321	(0.002)*	0.341	(0.021)*	0.290	(0.056)

Abbreviations: SD, standard deviation; IMT, intima-media thickness; LD, lumen diameter; WCSA, wall cross-sectional area; DD%, diameter distensibility (percentage); CSD%, cross-sectional distensibility (percentage); DC, diameter compliance; CSC, cross-sectional compliance; DD, diameter distensibility; IEM, incremental elastic modulus.

[a]IMT, IMT/LD, and WCSA measurements were only available for 24 subjects (13 females, 11 males).

[b]LD measurements were only available for 82 subjects (44 females, 38 males).

[c]IEM measurements were only available for 90 subjects (46 females, 44 males).

*Denotes statistical significance at $\alpha = 0.05$.

Table 7. Spearman Correlations Between Abdominal Aorta and Brachial Artery

Gender	Both		Female		Male	
Variable	**Rho**	**(*P*-value)**	**Rho**	**(*P*-value)**	**Rho**	**(*P*-value)**
IMT (mm)[a]	0.239	(0.309)	0.416	(0.203)	0.183	(0.637)
LD (mm)[b]	0.456	(<0.001)*	0.305	(0.044)*	0.560	(<0.001)*
IMT/LD[a]	0.127	(0.593)	0.145	(0.670)	0.217	(0.576)
WCSA (mm^2)[a]	0.313	(0.179)	0.782	(0.005)*	0.017	(0.966)
DD%	0.187	(0.072)	0.153	(0.300)	0.182	(0.232)
CSD%	0.230	(0.027)*	0.233	(0.111)	0.186	(0.220)
DC (mm/mmHg)	0.136	(0.194)	0.092	(0.535)	0.148	(0.331)
CSC1 (mm^2/mmHg)	0.172	(0.099)	0.138	(0.348)	0.197	(0.195)
CSC2 (1/mmHg)	0.137	(0.192)	0.112	(0.447)	0.166	(0.276)
IEM (mmHg)[c]	0.221	(0.037)*	0.221	(0.141)	0.239	(0.119)

Abbreviations: SD, standard deviation; IMT, intima-media thickness; LD, lumen diameter; WCSA, wall cross-sectional area; DD%, diameter distensibility (percentage); CSD%, cross-sectional distensibility (percentage); DC, diameter compliance; CSC, cross-sectional compliance; DD, diameter distensibility; IEM, incremental elastic modulus.

[a]IMT, IMT/LD, and WCSA measurements were only available for 20 subjects (11 females, 9 males).

[b]LD measurements were only available for 80 subjects (44 females, 36 males).

[c]IEM measurements were only available for 90 subjects (46 females, 44 males).

*Denotes statistical significance at $\alpha = 0.05$.

Figure Legend

Figure 1. Scatterplot for Carotid Artery and Abdominal Aorta DD% for all subjects (panel A), females only (panel B), and males only (panel C). Plots have been fit with a regression line (——), 95% confidence limits (■), and 95% prediction limits (– – –). (DD%=diameter distensibility percentage).

Figure 2. Scatterplot for Carotid Artery and Abdominal Aorta CSD% for all subjects (panel A), females only (panel B), and males only (panel C). Plots have been fit with a regression line (——), 95% confidence limits (■), and 95% prediction limits (– – –). (CSD%=cross-sectional distensibility percentage).

Figure 3. Scatterplot for Carotid Artery and Abdominal Aorta CSC2 for all subjects (panel A), females only (panel B), and males only (panel C). Plots have been fit with a regression line (——), 95% confidence limits (■), and 95% prediction limits (– – –). (CSC=cross-sectional compliance).

Figure 4. Scatterplot for Carotid Artery and Abdominal Aorta IEM for all subjects (n=90; panel A), females only (n=46; panel B), and males only (n=44; panel C). Plots have been fit with a regression line (——), 95% confidence limits (■), and 95% prediction limits (– – –). (IEM=incremental elastic modulus).

Figure 1. Plot for Carotid Artery and Abdominal Aorta DD%

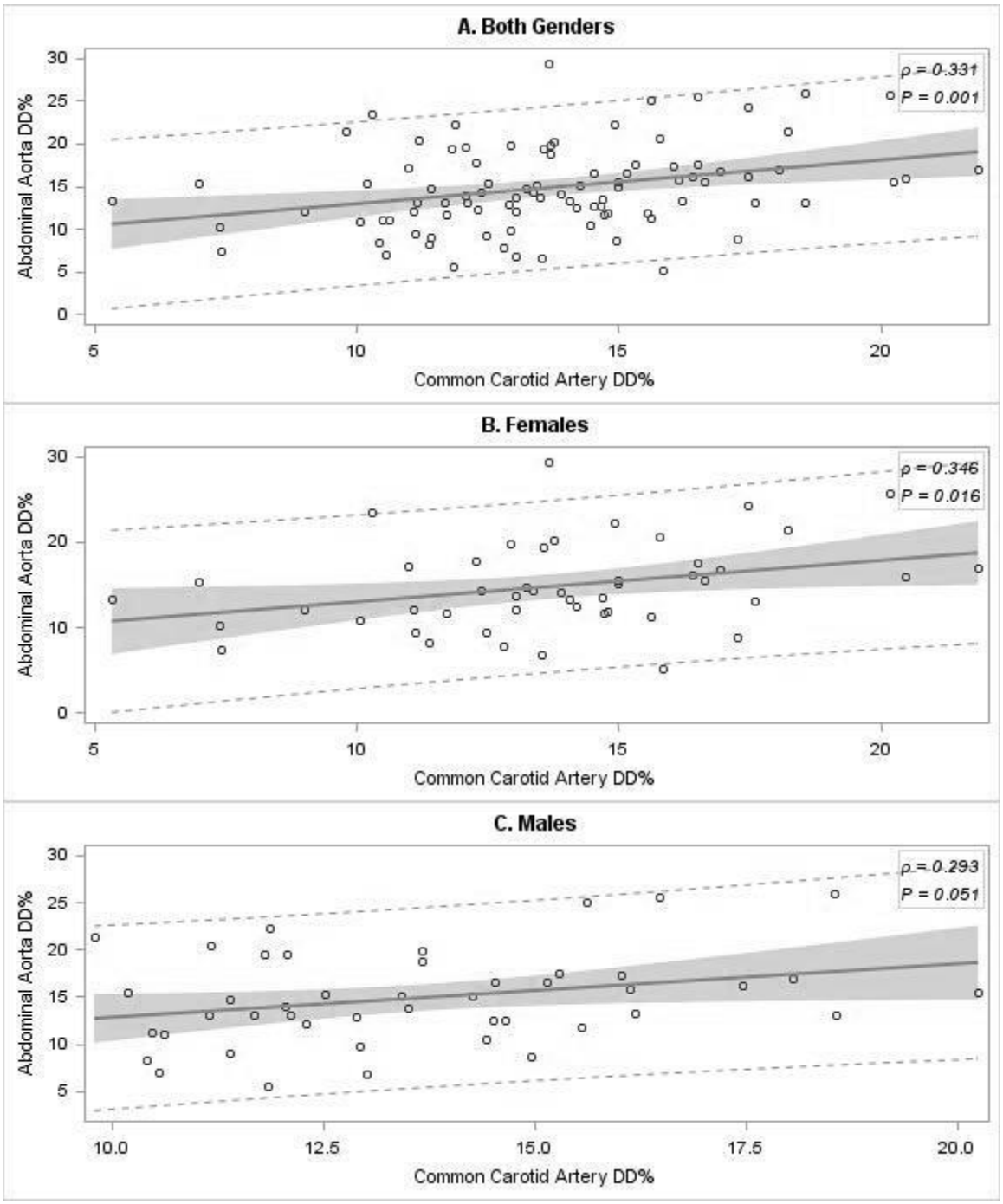


Figure 2. Plot for Carotid Artery and Abdominal Aorta CSD%

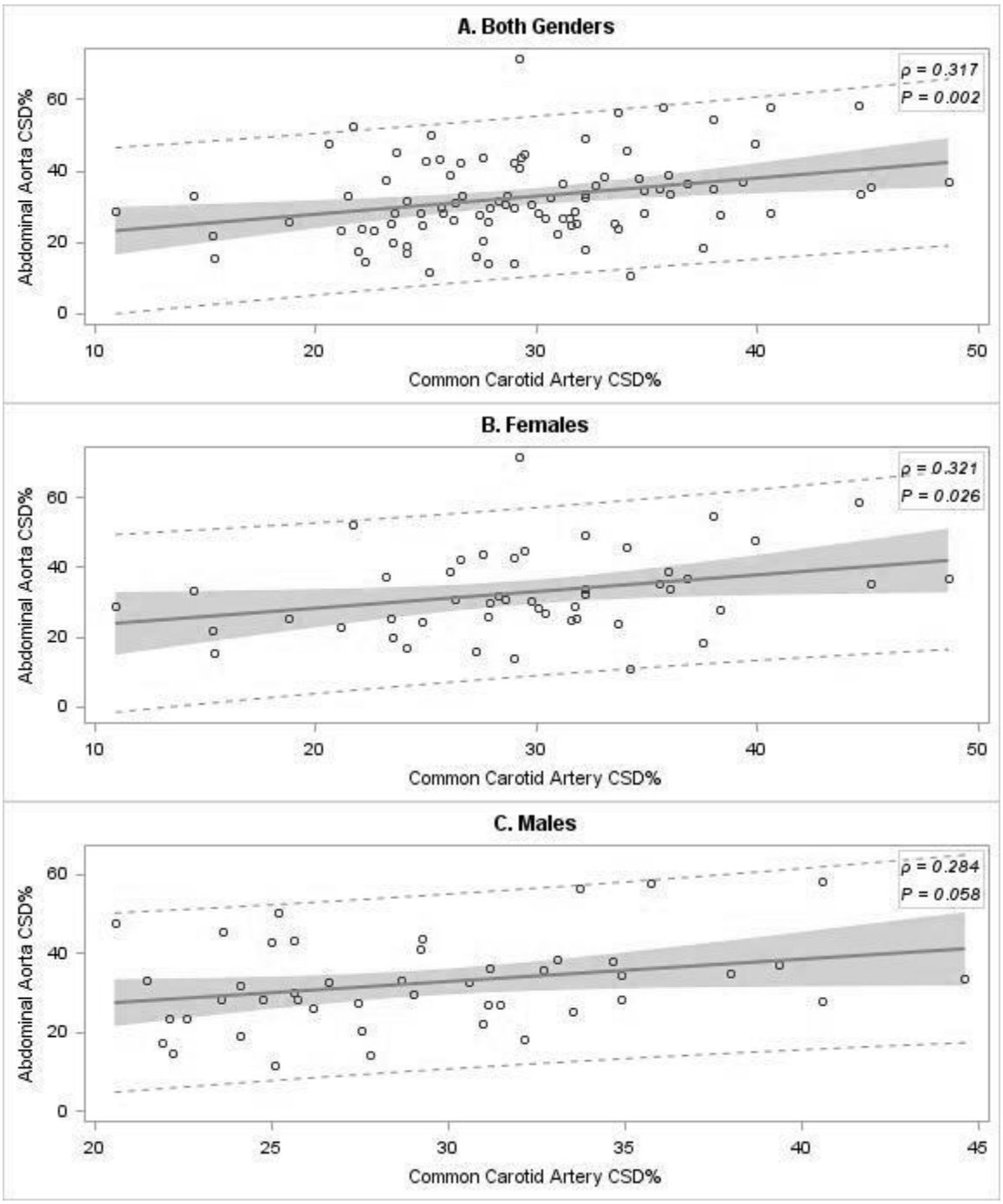


Figure 3. Plot for Carotid Artery and Abdominal Aorta CSC2

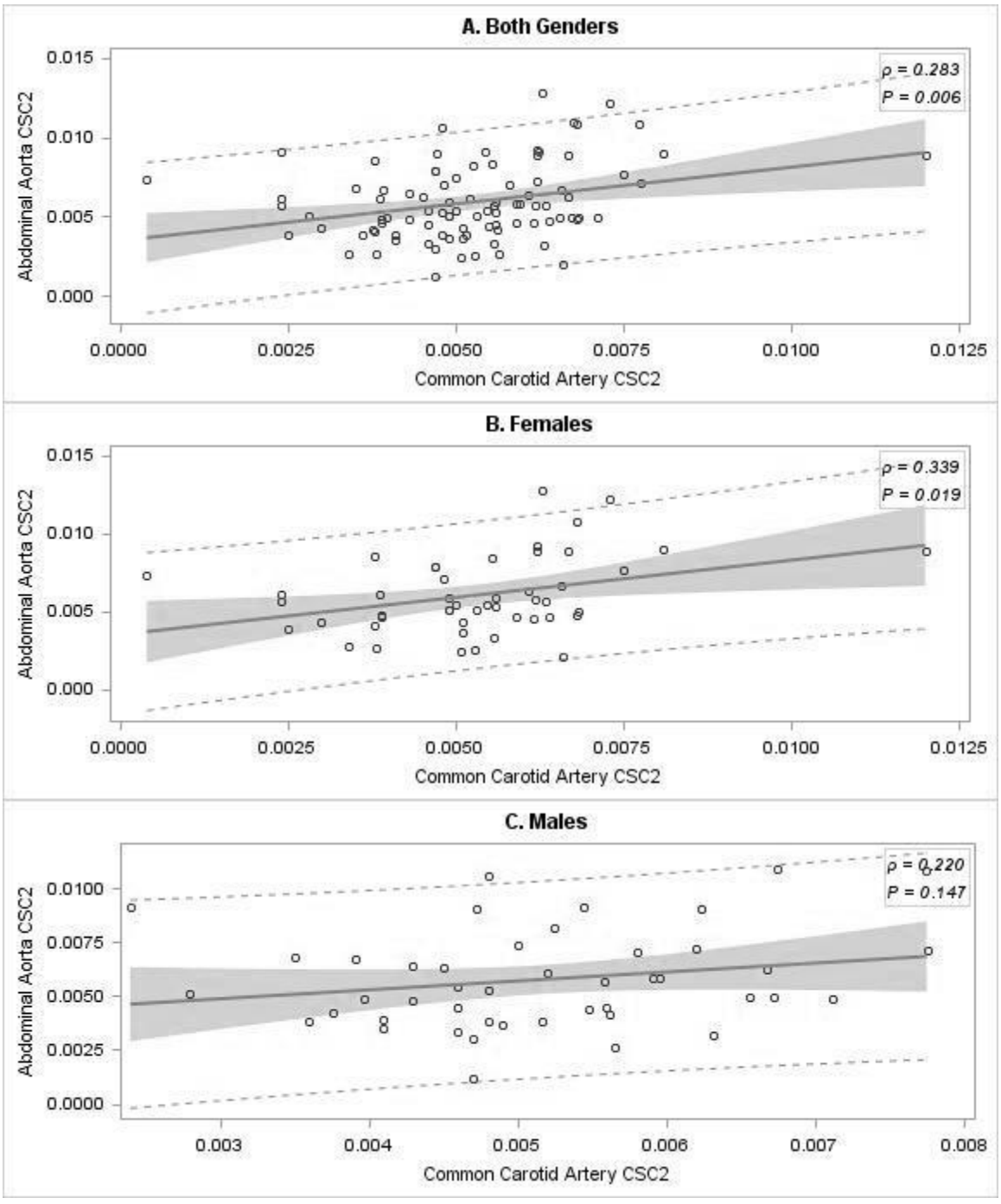
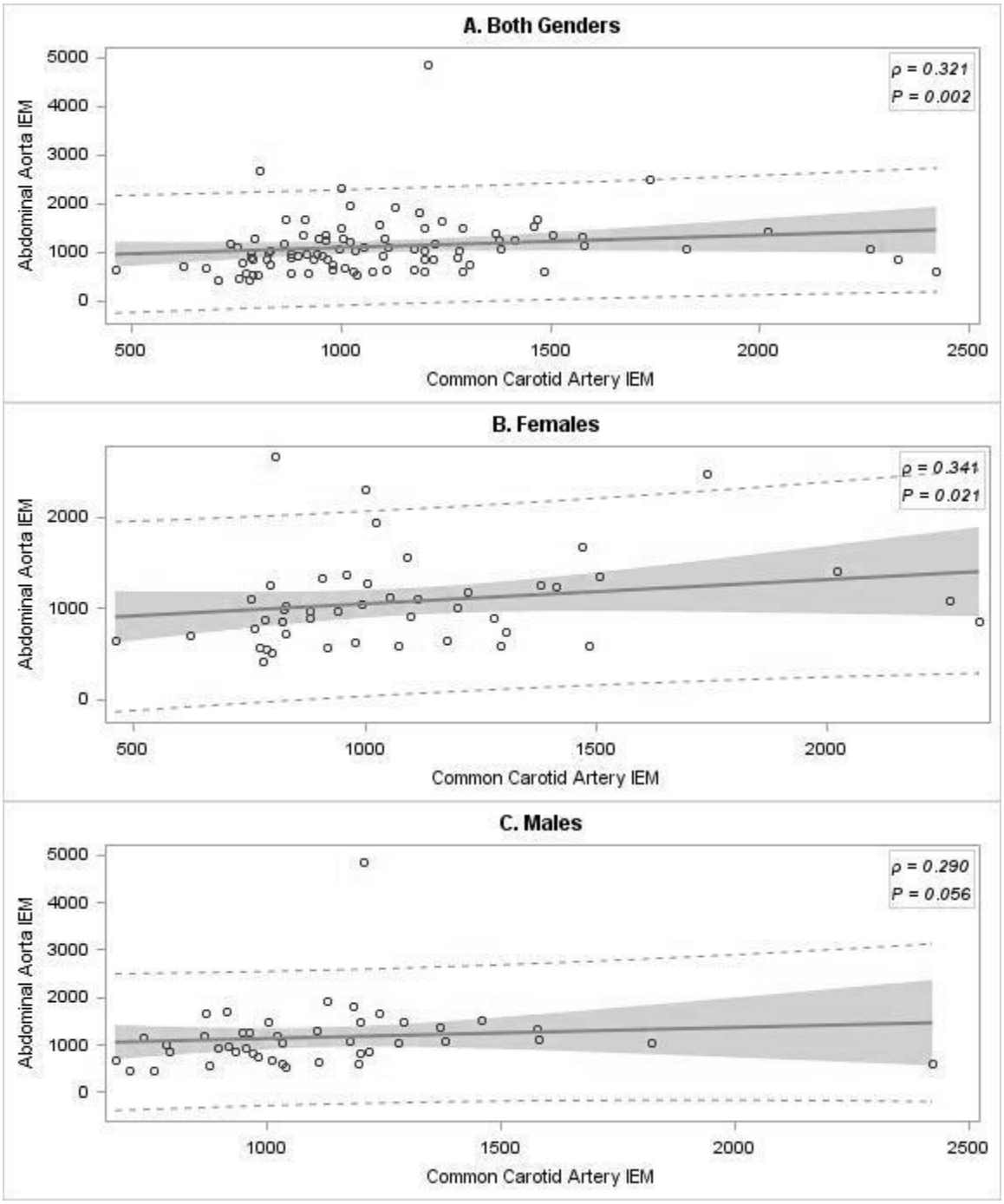


Figure 4. Plot for Carotid Artery and Abdominal Aorta IEM



CHAPTER 6. References

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