THE EFFECTS OF OVERWEIGHT AND AGE ON CARDIOVASCULAR HEALTH IN PRE AND POST PUBERTAL CHILDREN

A Thesis
by
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Abstract

THE EFFECTS OF OVERWEIGHT AND AGE ON CARDIOVASCULAR HEALTH IN PRE AND POST PUBERTAL CHILDREN

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Objective: To determine whether an increased trend in central aortic stiffness exists in children with increased adiposity when comparing groups from both pre-adolescents through adolescents. **Study Design:** 44 pre-adolescent (8.3 ± 1.5 y.o) and 32 adolescent (15.6 ± 1.8 y.o) participants were studied. Subjects came in for one observational visit consisting of body composition, body anthropometrics, aortic systolic blood pressure (ASBP), aortic pulse pressure (APP), heart rate (HR) and regional assessment of large artery stiffness using carotid-femoral pulse wave velocity (PWV_{CF}). The subjects and parental guardians were familiarized with the lab and assessment equipment prior to testing. **Results:** PWV_{CF} was higher in adolescent versus pre-adolescent for both normal weight (NW) and overweight children (OW) ($p < 0.01$). ASBP was higher in pre-adolescent versus adolescent in OW children ($p < 0.01$) and in adolescent versus pre-adolescent in NW children ($p < 0.05$). APP was higher in both pre-adolescent versus adolescent for OW children ($p < 0.05$). HR was lower in adolescent versus pre-adolescent for both NW and OW children ($p < 0.01$). **Conclusion:** Being OW seems to play less of a role with differences in PWV_{CF} between NW and OW groups and that puberty is the predominant factor responsible for increases in central stiffness in pediatrics.

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Last but not least, I would like to extend my thanks to all my friends who have been there through all the late nights and early mornings deliriously trying to think through seemingly impossible puzzles of the human body and the physiology that drives it.

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Forward

This thesis will be submitted to *The Journal of Pediatrics*, an international peer-reviewed journal owned and operated by Elsevier Inc.; it has been formatted according to the instructions to authors for that journal.

Abbreviations

Aortic pulse pressure (APP)

Aortic systolic blood pressure (ASBP)

Aortic diastolic blood pressure (ADBP)

Body mass index (BMI)

Brachial diastolic blood pressure (BDBP)

Brachial systolic blood pressure (BSBP)

Carotid-femoral pulse wave velocity (PWV_{CF})

Fat mass (FM)

Fat free mass (FFM)

Heart rate (HR)

Normal weight (NW)

Overweight (OW)

Introduction

Over the past four decades, childhood obesity has been shown to be increasing at an alarming rate and is becoming an epidemic health problem across the globe [1, 2]. It is now evident among current literature that pediatric obesity is correlated with the development of adult obesity and associated risk factors for cardiovascular diseases [3-5]. OW children and adolescents have gained increased attention due to the outward display of clinical physiognomies such as increased large artery stiffness and hypertension. Elevated blood pressure in children has been found to have a strong association with early vascular aging in regards to structural and functional abnormalities in conjunction with obesity and biological maturation [6-10]. Furthermore, obese children have been showing evidence of a rapid progression through puberty while accompanied by a multitude of adverse effects [11-14]. More importantly, previous research studying obesity and arterial stiffness has been performed without taking into account pubertal stages and body composition. This may exert inimical consequences in the progression of vascular aging as well as any future research being conducted within this field [15]. Thus, if children and adolescents are grouped according to pubertal age ranges, a better representation of the variability between subjects may be clearly identified.

Although it is rare that acute cardiovascular events are occurring in children and young adults, an increased awareness is warranted with central aortic stiffness due to the negative implications of obesity leading to hypertension in today's youth [16, 17]. Common measures utilized in order to assess central aortic stiffness is by measuring pulse wave velocity (PWV) in conjunction with techniques such as applanation tonometry [18, 19]. PWV

can be defined as the speed at which the forward pressure wave propagates from the aorta through the vascular tree. PWV_{CF} is commonly measured using the Sphygmocor device which has been implemented as the gold standard for assessing central arterial stiffness in both children and adults [20-22]. A faster waveform or one with increased PWV has been shown to be indicative of increased arterial stiffness due to decreased elasticity, while a slower waveform may represent a healthier more elastic set of arteries. However, even though there is an absence of normative data for comparison among pediatrics, the ideology for the assessment of arterial stiffness remains consistent [23]. The employment of non-invasive measurements of central aortic health is of pinnacle importance due to central arterial stiffness being recognized as an independent risk factor for the early development of coronary artery disease. The purpose of this study was to assess how OW children and pubertal development affect cardiovascular health from pre-adolescents through adolescents. This study aims at advancing pediatric knowledge in the realm of cardiovascular health and OW children in order to build better forecast models which will help prevent and predict negative adaptations at an earlier age. We hypothesized that OW children would display stiffer arteries compared to NW children in both pre-adolescents and adolescents.

Subjects and Methods

Study population

44 pre-adolescent (8.2 ± 1.5 y.o) and 32 adolescent (15.6 ± 1.8 y.o) participated in this study. Among the pre-adolescent group, there were 16 male and 28 female (13 males and 18 females in the NW group, 3 males and 10 females in the OW group). Among the adolescent group, there were 16 male and 16 female (9 males and 13 females in the NW group, 7 males and 3 females in the OW group).

Children were recruited from the local community and from the local school system. Subjects were grouped according to the defined children and adolescent age ranges set by the World Health Organization and were not separated by sex. There was no control for female menstrual cycle. Both the children and parents/guardians gave written informed consent for the project, which was approved by the Ethics Committee of Appalachian State University. Subjects were admitted to the study if they were between the ages of 7 and 17 years of age. Children $\geq 85^{th}$ percentile or higher based on BMI were placed in the OW group and in the NW group if they were $\leq 85^{th}$ percentile based on BMI. All subjects were not taking any medications or had any medical conditions including diabetes, heart, respiratory or renal disease as reported on the health history questionnaire. Participants and their parents were asked to avoid drinks containing caffeine such as soft drinks or soda 3 hours before the test, not perform exercise the day of the test or eat large meals 4 hours prior to the test. Assessments were performed in the Pediatric Exercise Physiology laboratory, Boone NC and at the Hardin Park Elementary School, Boone NC. Total time required for the measurements was approximately 1.5 hours. Measurements were performed between 8:00 to 11:00 AM or 4:00 to 6:00 PM.

Anthropometric Measurements

Upon arrival, subjects were instructed to remove their shoes before height and weight was measured using a wall mounted stadiometer and a digital floor scale (SECA Technology, Germany) with values rounded to the nearest centimeter (cm) and tenth of a kilogram (kg). Hip and waist circumference was obtained by instructing the subject to stand up straight and breathe out to reduce abdominal inflation. A tape measure was used to measure around the smallest part of the subject's waist, slightly above the belly button. A tape measure was then used to measure the distance around the largest part of the subject's hips, around the widest point of the subject's gluteal region to the nearest cm. All procedures were followed in accordance with the World Health Organization Geneva expert consultation, 2008.

Body Composition

Fat mass (FM) and fat free mass (FFM) was assessed in subjects that reported to the laboratory by using air displacement plethysmography (Bodpod technology, COSMED, Italy) or by bioelectrical impedance analysis (Rudolph J. Liedtke systems, Michigan) in order to assess children at school. For bioelectrical impedance analysis, subjects were instructed to remove their shoes, supine on a cushioned table. Electrodes were then placed over the right ulnar head and ring finger as well as over the right medial malleolus and index toe before collecting FM and FFM values. Subjects wore tight fitting clothes, a swimmers cap, and no shoes or jewelry. Weight (kg) was obtained using a floor scale before stepping inside the chamber with their feet flat on the floor, hands flat on their thighs and were instructed to remain as still as possible for the 45 – 60 sec. test duration. This measurement was taken twice and the average calculated between the two to ensure accuracy.

Arterial Stiffness

Resting blood pressure. Blood pressure and PWV_{CF} values were obtained using the Sphygmocor Excel module (SphygmoCor® technology, Sydney, Australia). The pulse wave analysis (PWA) function was used to measure brachial blood pressure, ASBP. APP. and HR. Brachial blood pressure was taken after five minutes of quiet rest lying supine with dim lighting on the right arm. Three measurements were made at 2-minute intervals and the mean was used for analysis.

PWV. After an additional 2-minutes of rest a blood pressure cuff was positioned around the middle of the right thigh. The right carotid artery was located by palpation of the neck and marked lightly to maintain its location. Once located, three separate measurements were taken to determine vascular distance (cm); 1. Carotid artery to sternal notch, 2. Sternal notch to cuff, 3. Femoral pulse to cuff. This measurement was taken in triplicate with the average used for analysis. Each subsequent measurement was taken with minimal time between. Valid waveform consistency and amplitude were assessed for passing quality control before an average was taken to ensure accuracy between trials. If values differed by more than ± 0.3 m/s, an additional measurement was performed.

Statistical Analysis

Comparisons were assessed using a repeated measures ANOVA and followed up with an independent samples T-test when significant to discern differences between groups. All analyses were performed using PRISM, Graphpad Software. The level of significance was set at $p < 0.05$. Results are expressed as mean ± SD.

Results

Seventy-six subjects were included in this study. See table 1 for subject characteristics. PWV_{CF} differences between pre-adolescent and adolescent NW was 4.0 ± 0.5 vs. 5.0 ± 0.7 m/s ($p < 0.01$) (Figure 1). Differences in PWV_{CF} between pre-adolescent and adolescent OW was 4.2 ± 0.5 vs. 5.0 ± 0.8 m/s ($p < 0.05$) (Figure 1). ASBP differences between pre-adolescent NW and adolescent NW was 90.7 ± 8.1 vs. 96.1 ± 6.9 mmHg ($p < 0.05$) (Figure 2). Differences in ASBP between pre-adolescent NW and OW was 90.7 ± 8.1 vs. 100.1 ± 6.0 mmHg ($p < 0.01$) (Figure 2). APP differences between pre-adolescent NW and OW groups was 77.0 ± 7.2 vs. 82.3 ± 5.1 mmHg ($p < 0.05$) (Figure 3). HR differences between pre-adolescent and adolescent NW groups was 79 ± 13.3 vs. 67 ± 10.4 bpm ($p < 0.01$) (Figure 4). Differences in HR between pre-adolescent and adolescent OW groups was 81 ± 9.2 vs. 72 ± 5.9 bpm ($p < 0.01$) (Figure 4).

Table 1

Descriptive characteristics of subjects.

	Normal Weight		
Characteristics	Preadolescent (n = 31)	Adolescent (n = 22)	*P* value
Age (years)	8.1 ± 1.4	13.9 ± 4.2	< 0.01
Height (cm)	129.5 ± 9.1	167.0 ± 10.2	< 0.01
Weight (kg)	26.8 ± 5.4	58.4 ± 9.2	< 0.01
BMI (kg/m^2)	15.9 ± 1.4	20.8 ± 2.0	< 0.01
FM (%)	21.0 ± 7.3	21.7 ± 7.9	0.75
FFM (%)	79.0 ± 7.3	78.3 ± 7.9	0.71
ADBP (mmHg)	63.2 ± 7.1	64.2 ± 7.2	0.60
AMAP (mmHg)	72.4 ± 7.0	74.9 ± 6.8	0.19
BSBP (mmHg)	105.1 ± 9.8	111.3 ± 7.6	0.01
BDBP (mmHg)	62.0 ± 6.2	63.7 ± 7.4	0.38

BMI, Body mass index; FM, fat mass; FFM, fat free mass, ADBP, aortic diastolic blood pressure; AMAP, aortic mean arterial pressure; BSBP, brachial systolic blood pressure; BDBP, brachial diastolic blood pressure. All data are reported as mean ±.

Table 2

Descriptive characteristics of subjects.

	Overweight		
Characteristics	Preadolescent (n = 13)	Adolescent (n = 10)	*P* value
Age (years)	8.7 ± 1.8	12.8 ± 4.3	< 0.01
Height (cm)	139.7 ± 13.0	166.0 ± 14.3	0.0003
Weight (kg)	45.0 ± 15.6	79.3 ± 24.2	0.002
BMI (kg/m^2)	22.3 ± 3.9	28.2 ± 4.3	0.003
FM (%)	38.6 ± 7.7	33.8 ± 11.2	0.21
FFM (%)	61.4 ± 7.7	66.2 ± 11.2	0.22
ADBP (mmHg)	64.4 ± 5.3	66.3 ± 6.7	0.49
AMAP (mmHg)	76.3 ± 5.0	78.4 ± 6.7	0.57
BSBP (mmHg)	113.0 ± 7.7	116.9 ± 10.5	0.38
BDBP (mmHg)	64.1 ± 5.2	65.2 ± 7.6	0.77

BMI, Body mass index; FM, fat mass; FFM, fat free mass, ADBP, aortic diastolic blood pressure; AMAP, aortic mean arterial pressure; BSBP, brachial systolic blood pressure; BDBP, brachial diastolic blood pressure. All data are reported as mean ± SD.

Table 3

Descriptive characteristics of subjects.

	Preadolescent		
Characteristics	Normal Weight (n = 31)	Overweight (n = 13)	*P* value
Age (years)	8.1 ± 1.4	8.7 ± 1.8	0.69
Height (cm)	129.5 ± 9.1	139.7 ± 13.0	0.01
Weight (kg)	26.8 ± 5.4	45.0 ± 15.6	0.0007
BMI (kg/m^2)	15.9 ± 1.4	22.3 ± 3.9	< 0.01
FM (%)	21.0 ± 7.3	38.6 ± 7.7	< 0.01
FFM (%)	79.0 ± 7.3	61.4 ± 7.7	< 0.01
ADBP (mmHg)	63.2 ± 7.1	64.4 ± 5.3	0.49
AMAP (mmHg)	72.4 ± 7.0	76.3 ± 5.0	0.29
BSBP (mmHg)	105.1 ± 9.8	113.0 ± 7.7	0.005
BDBP (mmHg)	62.0 ± 6.2	64.1 ± 5.2	0.19

BMI, Body mass index; FM, fat mass; FFM, fat free mass, ADBP, aortic diastolic blood pressure; AMAP, aortic mean arterial pressure; BSBP, brachial systolic blood pressure; BDBP, brachial diastolic blood pressure. All data are reported as mean ± SD.

Table 4

Descriptive characteristics of subjects.

	Adolescent		
Characteristics	Normal Weight (n = 22)	Overweight (n = 10)	*P* value
Age (years)	13.9 ± 4.2	12.8 ± 4.3	0.14
Height (cm)	167.0 ± 10.2	166.0 ± 14.3	0.83
Weight (kg)	58.4 ± 9.2	79.3 ± 24.2	0.02
BMI (kg/m^2)	20.8 ± 2.0	28.2 ± 4.3	0.0003
FM (%)	21.7 ± 7.9	33.8 ± 11.2	0.008
FFM (%)	78.3 ± 7.9	66.2 ± 11.2	0.009
ADBP (mmHg)	64.2 ± 7.2	66.3 ± 6.7	0.45
AMAP (mmHg)	74.9 ± 6.8	78.4 ± 6.7	0.18
BSBP (mmHg)	111.3 ± 7.6	116.9 ± 10.5	0.16
BDBP (mmHg)	63.7 ± 7.4	65.2 ± 7.6	0.61

BMI, Body mass index; FM, fat mass; FFM, fat free mass, ADBP, aortic diastolic blood pressure; AMAP, aortic mean arterial pressure; BSBP, brachial systolic blood pressure; BDBP, brachial diastolic blood pressure. All data are reported as mean ± SD.

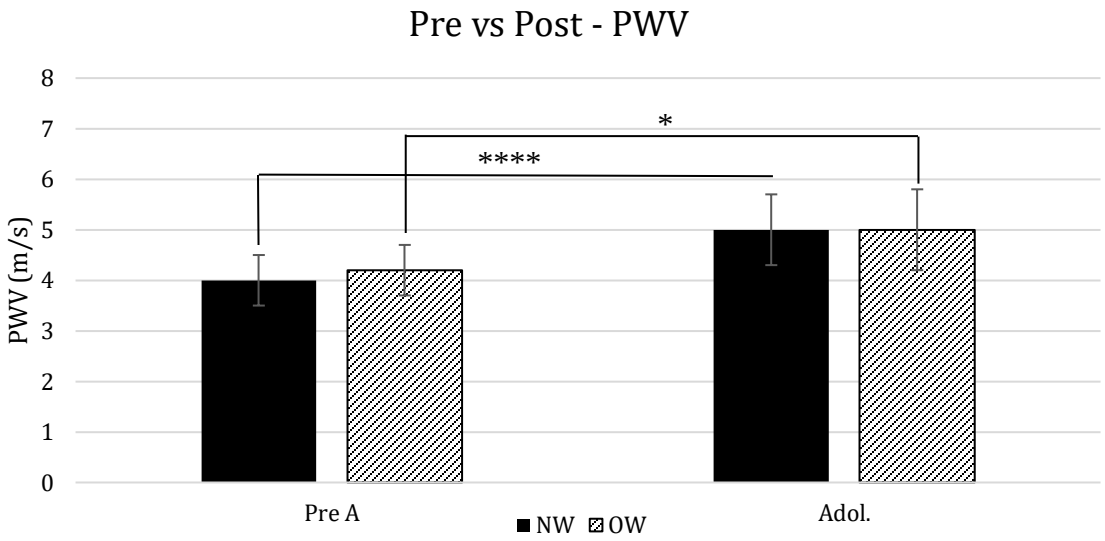

Fig. 1. Differences in PWV_{CF} between pre-adolescent and adolescent groups. * $p < 0.05$; **** $p < 0.0001$.

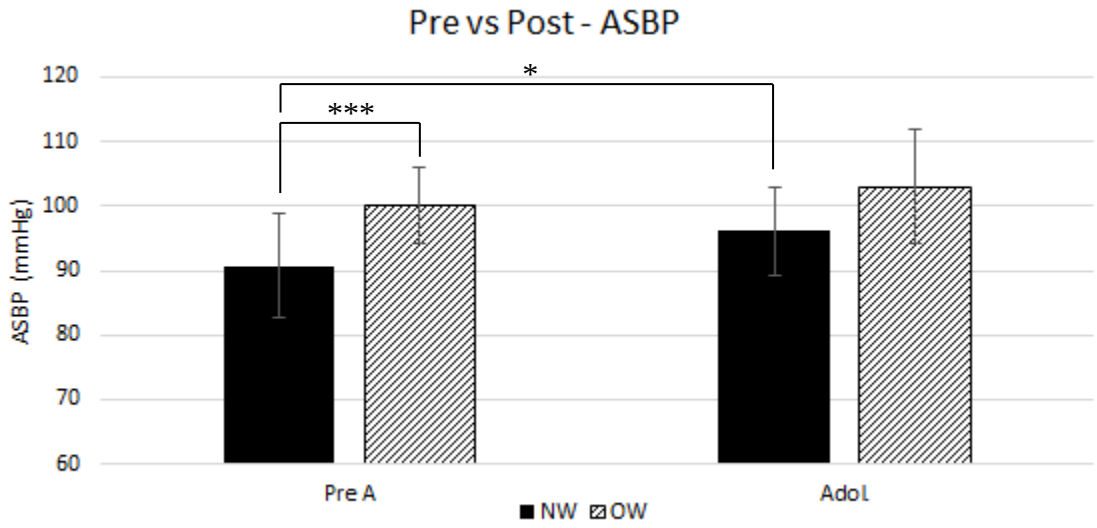

Fig. 2. Differences in ASBP between pre-adolescent and adolescent groups. * $p < 0.05$; *** $p < 0.001$.

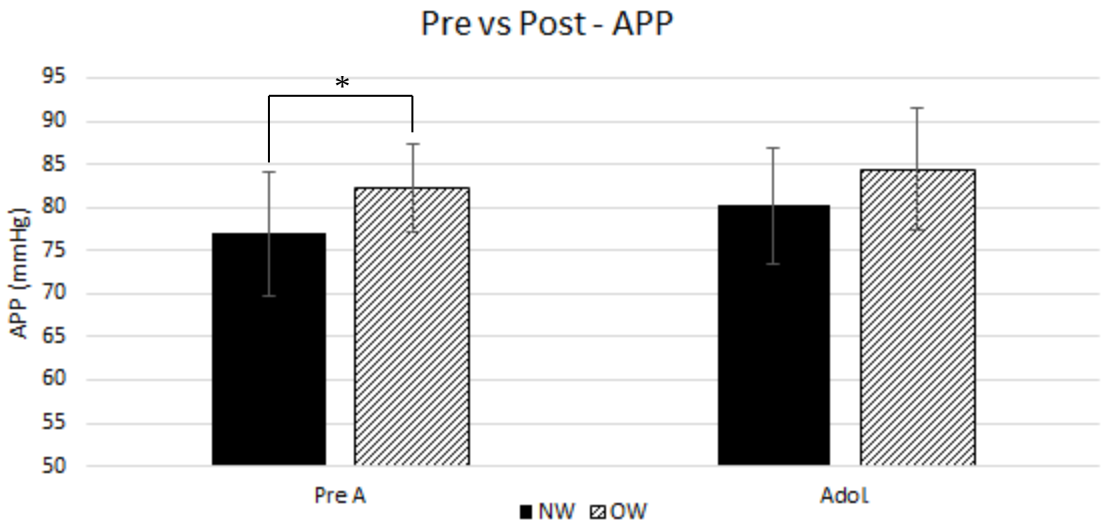

Fig. 3. Differences in APP between pre-adolescent and adolescent groups. * $p < 0.05$.

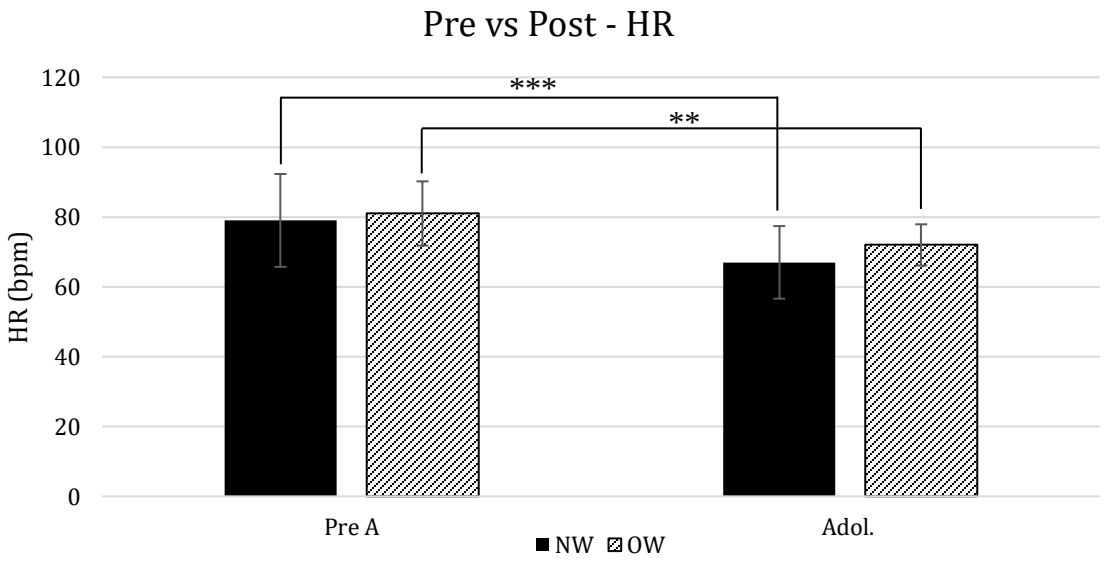

Fig. 4. Differences in HR between pre-adolescent and adolescent groups. ** $p < 0.01$; *** $p < 0.001$.

Discussion

The purpose of this study was to assess how puberty and body weight affect cardiovascular health in children. The novel finding of this study was that ASBP was higher with the pre-adolescent group in OW children compared to their NW counterparts, and that puberty results in an increase in central stiffness while being OW does not increase large artery stiffness. Our findings are in line with previous literature showing OW children displaying higher ASBP when compared to NW children and that pubertal hormones can affect vasculature compliance [24, 25]. Moreover, our findings show there is no difference in arterial stiffness between OW and NW children, which is in contrast with some of the present literature [15]. It is well known that PWV in the adult population increases in a linear fashion with age [26]. However, in pediatrics, the influence of age and its effects on arterial stiffness have been less established and could be largely perplexed by pubertal status [27-29]. The higher PWV_{CF} observed in the adolescent children may be representative of pubertal progression being modulated by hormonal effects between groups [30, 24, 25].

Present studies report contradicting results alluding to the proposed mechanisms of increased arterial stiffness and the role that childhood obesity plays in its progression. Elevated blood pressure and hypertension is a well-documented finding in children with obesity and has also been shown to be associated with an increase with PWV in adults [31, 32]. Our results reported an elevated ASBP in the pre-adolescent OW group compared to their NW counterparts, suggesting increased adiposity to be a primary factor affecting blood pressure. There was no differences found with PWV_{CF} between NW and OW subjects which may be indicative of other underlying mechanisms responsible for the increase in blood pressure. Increased vascular volume can cause an increase in blood pressure with minimal to

no changes in PWV in obese children [33, 34]. An augmented stroke volume (SV) can facilitate increases in systolic blood pressure in the large central arteries without increases in arterial stiffness [33]. This hypothesis is supported by the increased APP and decreased HR without concomitant increases in PWV_{CF} in the OW subjects. It has been shown that increases in APP could be explained by increases in stroke volume and cardiac output [35]. Furthermore, past literature shows increased vessel length in conjunction with increased adiposity can cause a likely increase in total peripheral resistance (TPR) [36, 37]. Thus, in combination from the previously stated vascular components, increases may be seen in ASBP and ultimately consequential increases in arterial stiffness. The latter may also beget the onset of elevated blood pressure or hypertension as seen in both longitudinal adult studies and animal models [27, 38]. Longer periods of higher blood pressure can increase arterial stiffness which is directly correlated to the aging process. Therefore, elevated ASBP from childhood may cause early vascular aging which may accelerate the process of arterial stiffness in adults causing hypertension [34, 39]. Longitudinal investigations are needed to merit an explanation for this phenomenon in pediatrics.

During the normal progression of childhood development in regards to vascular formation, vessels go through two major physiological changes, dilation and stiffening [40, 41]. Parallel to our findings, there have been reported normal to lower measures of arterial stiffness in obese children with elevated blood pressure when compared to healthy controls [33, 26]. A reduction in PWV in OW children may be found in conjunction with an increase in vessel diameter in early childhood development. Although, when the natural adaptations are outpaced by an increased central arterial stiffness, an increase in PWV can be observed

allowing for a clear identification to be made between normal and pathologic progression among children.

Investigators have attempted to justify the relationship that obesity has in regard to maturational progression. As previously stated, the primary finding of this study was the higher ASBP in OW pre-adolescent children compared to their NW counterparts, and the higher PWV_{CF} in preadolescents. Sex differences may play a role in the facilitation of vascular effects observed in the current study, although sex differences were not accounted for. Past studies have shown central large arteries becoming stiffer in males and more compliant in females due to the effects of testosterone and estrogen release during puberty [10]. Thus, a blunting effect within groups could be responsible for the minimal differences seen with PWV_{CF} due to both males and females being grouped together. On the contrary, it has been shown that arterial stiffness increases in a linear fashion parallel to adult studies without sex differences serving as an underpinning for vascular variations [42].

Due to the multifaceted nature of studying cardiovascular parameters in pediatrics, there are limitations that need to be addressed. First and foremost, subjects were not separated by sex or biological age. Second, a group of pre-adolescent subjects were tested at school while the rest of the subjects were tested in our laboratory. Third, a sufficient number of subjects was not reached in order to achieve numbers for sufficient power which may be attributed to a lack of significance in the adolescent group between weight groups ($p < 0.063$). Future studies may merit significant differences with a greater subject size in conjunction with being able to control factors such as puberty, sex, and menstrual cycle.

ASBP was higher with the pre-adolescent group in OW children compared to their NW counterparts indicating that being OW plays a strong role on central blood pressure in

children. Puberty was also found to be the predominant factor in facilitating increases in central arterial stiffness regardless of weight status. This suggests that hormonal release and morphology changes during puberty may modulate large artery stiffness. Future studies are needed in order to investigate the effects of sex differences and pubertal status on central stiffness. Recognizing whether the subjects were or already have experienced puberty as well as being able to control for menstrual cycle will provide important information eluding to the effects of age and OW status with cardiovascular health in clinical pediatrics.

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Vita

Austin Lassiter as born in Pembroke Pines, Florida, to Melissa and Wes Lassiter. He attended First Flight High School in Kill Devil Hills, North Carolina, and graduated in May 2007. In the fall of 2015, he began attending Appalachian State University where he majored in Exercise Science. After graduating in May 2017, he immediately began two graduate assistantships in both research and with cardiopulmonary rehabilitation in the Exercise Science department at Appalachian State University and began studying toward a Master of Science degree. In August 2019, Austin will be graduating with a Master of Science.