MEASURES OF EJECTION DURATION IN NORMAL WEIGHT AND OVERWEIGHT ADOLESCENT CHILDREN

A Thesis
by
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Abstract

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Purpose: To determine how measures of ejection duration, subendocardial viability ratio, and central arterial health are affected by the overweight condition in a sample of adolescent children. **Methods:** 34 sex and age-matched adolescent children were studied, with half of the total sample (17, 11 male, 6 female) classified as overweight (OW). In one laboratory visit, anthropometric measures (height, weight, body mass index), body composition analysis (body fat percentage), and non-invasive measures of central cardiovascular health, including resting heart rate (HR), aortic systolic (ASBP), diastolic (ADBP), mean arterial (AMAP) and pulse (APP) pressures, carotid-femoral pulse wave velocity (cf-PWV), ejection duration in milliseconds (EDms) and relative to the heart rate period (ED%), and the subendocardial viability ratio (SEVR) were performed. **Results:** As expected, OW adolescents weighed significantly more, had a higher body mass index, and a greater body fat percentage than normal weight (NW) adolescents. cf-PWV was significantly higher in OW compared to NW participants (5.1 m/s ± 0.9 m/s vs. 4.5 m/s ± 0.5 m/s respectively; $F(1,32) = 6.558$, $p = 0.015$, Cohen's $d = 0.88$). OW adolescents also reported significantly higher values for ASBP (103.1 mmHg ± 11.8 mmHg vs. 95.7 mmHg ± 8.2 mmHg respectively; $F(1,32) = 4.444$, $p = 0.043$, Cohen's $d = 0.72$) and significantly lower values of SEVR (114.4 % ± 25.9 % vs. 132.2 % ± 22.0 % respectively; $F(1,32) = 4.663$, $p = 0.038$; Cohen's $d = 0.33$). Measures of EDms, ED%, HR, AMAP, ADBP and APP were not significantly different between groups despite a positive trend in mean values and moderate effect sizes for both HR and ED%. **Conclusion:** The overweight condition in adolescence is marked by unfavorable changes in cardiovascular health as measured by cf-PWV, ASBP, and SEVR. Although significant differences were not found, our observations indicate that the ED% may still lend to the assessment of CVD risk in a larger sample with more obese adolescents.

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Introduction

Recognized by the World Health Organization as a major global health issue, the rising prevalence of obesity carries both contemporary and future consequences (Lobstein et al., 2004; Olshansky et al., 2005). Of particular concern is the incidence of obesity in childhood, which despite an attenuated rate of increase over the last decade remains a significant public health issue (Hales et al., 2017). Well-established as a risk factor for the development of cardiovascular disease (CVD), obesity is a unfavorable condition, as excessive adiposity increases the risk profile for co-morbid conditions including hypertension, type 2 diabetes, coronary artery disease, and dyslipidemia (Brown et al., 2000; Hubert et al., 1983). These associations are observed traditionally in obese adults, yet mounting evidence suggests that obesity in childhood leads to the development of the same risk factors for disease as adults (Freedman et al., 2007; Tu et al., 2011; Xi et al., 2017).

Compared to their lean peers, overweight and obese children report significantly elevated systolic (SBP) and diastolic (DBP) blood pressures and demonstrate a serious risk of future obesity and hypertension with age (Brady, 2017; Ewald & Haldeman, 2016; Must & Strauss, 1999). In a cohort study of over 100,000 children 3-17 years old, BMI category was significantly associated with increases in SBP and DBP percentiles across all age-gender groups, and obese preadolescent children were significantly more likely to present with hypertension at a 3-year follow-up (Parker et al., 2016). Hypertensive children are also more likely to have left ventricular hypertrophy (Brady et al., 2008), greater arterial stiffening (Tounian et al., 2001) and advanced vascular aging (Le et al., 2010).

The rising incidence of childhood obesity and hypertension carries the potential to change conventional standards of disease progression, increasing the incidence of cardiovascular diseases in earlier stages of life. To combat this emerging issue, investigations employing non-invasive measures of cardiac function should be undertaken in order to identify measures with potential pre-diagnostic value in pediatrics. An approach recommended by the American Heart Association is the analysis of arterial pulse waveforms, which can estimate central arterial pressure, as well as the assessment of pulse wave velocity (PWV), a well-established clinical measurement of arterial stiffness (Urbina et al., 2009). Technologies such as Sphygmocor (AtCor Medical, Australia) are capable of measuring both pulse wave analysis (PWA) and PWV and have introduced clinically relevant product lines such as the XCEL that reduce operator-dependence by minimize the technical skill required (Butlin & Qasem, 2016).

The minimally intrusive nature of PWA and PWV measurement makes these methods of cardiovascular assessment ideal for use in a pediatric research setting. Along with the established measures of central arterial pressure and stiffness, novel indicators of cardiovascular health and function are also measurable, the explorations into which are warranted to determine their pre-diagnostic value in a subclinical pediatric cohort. Of particular interest, is the evaluation of the ejection duration (ED). Also denoted historically as the left ventricular ejection time (LVET), ED is defined as the time in the cardiac cycle during which the left ventricle actively ejects blood through the aortic valve into circulation (Hassan & Turner, 1983). ED is measurable as either an absolute time, usually in milliseconds (EDms), or as a relative percentage of the total heart rate period (ED%). ED is measured non-invasively using arterial pulse wave analysis, and it is more accurately assessed when central aortic waveforms are used (Lewis et al., 1977; Obata et al., 2017). The ED has demonstrated value as a CVD risk assessment in longitudinal studies (Biering-Sørensen et al., 2018; Haiden et al., 2014) and in the progression of heart failure (Garrard Jr et al., 1970). Previous work on ED within a pediatric population is scarce, and to date, little work has been performed regarding the association of adiposity to ED.

Another measure that considers the ED in the context of aortic pressure and may be of clinical utility in a pediatric cohort is the subendocardial viability ratio (SEVR, also cited historically as the Buckberg index). Referencing the central aortic pressure waveform, the SEVR uses the systolic and diastolic area under the curve (AUC), identifying the diastolic pressure-time area as a surrogate for myocardial oxygen supply, and the systolic pressure-time area as a surrogate for myocardial oxygen demand (Buckberg et al., 1972). The subsequent ratio (diastolic pressure-time area/systolic pressure-time area) generates an estimated myocardial supply-demand ratio. Although myocardial ischemia is not a concern for overweight and obese children, the SEVR can effectually be used to assess the resting workload of the heart, which is shown to be higher in overweight and obese individuals (Masuo et al., 2000). As the SEVR has been shown a clinically useful parameter in adults (Aslanger et al., 2017; Salvi et al., 2013; Scandale et al., 2018; Smith et al., 2012), explorations into pediatric cohorts are warranted.

The purpose of this study is to determine how measures of ejection duration, SEVR and central arterial health are affected by the overweight condition in a sample of adolescent children in order to better understand the utility of these measures in the evaluation and prevention of cardiovascular disease.

It is hypothesized that:

Hypothesis #1: Measures of ED relative to the total heart rate period will be longer in overweight compared to normal weight adolescents.

Hypothesis #2: Measures of aortic pressure and PWV will be higher and the SEVR lower, adolescents who are overweight.

Methods

Study Population

Data collection for this study was performed as a part of the Pediatric Observational Study (POS), an ongoing longitudinal and cross-sectional study that has been approved by the Appalachian State University Institutional Review Board. We recruited healthy boys and girls ages 11-17 years currently unmedicated and without signs and symptoms of medical conditions including diabetes, heart, respiratory or renal disease. In order to investigate the differences between normal weight (NW) and overweight (OW) adolescents, BMI was used as the primary grouping variable. Using the CDC BMI-for-age percentile chart, children with a BMI greater than or equal to the 85^{th} percentile of their age-and-sex-matched population were classified as OW and all children below the 85^{th} percentile classified as NW.

In the POS, data on sixty-two adolescent children had been collected. Of the dataset, seventeen participants (11 male, 6 female) were classified as OW by the CDC reference and lead to an unequal sample size between groups. In order to maintain samples of comparative size, and to eliminate bias during selection, each OW participant was matched with a NW counterpart primarily by sex and secondarily by age recorded at the time of testing. When multiple NW participants qualified for inclusion (e.g. three NW, 16-year-old males available to pair with one 16-year-old OW male), the proximity of birthday to the OW participant was used as the determining factor.

Participants in this study were a multi-ethnic sample of members in the local community as well as from various regions of North Carolina. Participants and their parental guardians were required to read and sign a written informed consent to participate in research. All procedures alongside the benefits and risks of the study were explained to participants, and their written informed consent was obtained from the parents before participation. All tests were conducted in the Pediatric Exercise Physiology Laboratory within the Department of Health and Exercise Science at Appalachian State University (Boone, NC, United States). The same protocol was used for all participants.

Anthropometrics and Body Composition

Upon arrival at the lab, anthropometric measurements and body composition tests were performed. Height was measured with a wall mounted stadiometer to the nearest 0.1 cm, and body weight was measured with a digital floor scale to the nearest 0.1 kg (SECA Technology, Germany). These measures were used in the calculation of BMI (BMI = weight, kg / height, m^2). Body composition was assessed via air displacement plethysmography (BodPod, COSMED, Italy) using the Siri equation and with the thoracic gas volume estimated. Subjects were instructed to wear tight fitting clothes, wore a rubber swimmers cap, and did not have on shoes or jewelry prior to the measurement. Participants were instructed to sit with upright posture inside the BodPod chamber with feet flat on the floor, hands flat on their thighs and to remain still and breathe normally for the 45 – 60 second test duration. Two measurements of body fat percentage (%FM) were taken, and the average value was reported.

Cardiovascular Measurement

All cardiovascular measurements were obtained from the automated Sphygmocor XCEL (AtCor Medical, Sydney Australia), from which the tests of pulse wave analysis (PWA) and carotid-femoral pulse wave velocity (cf-PWV) were performed.

Measurement of Pulse Wave Analysis

In a dimly lit room, participants laid supine on a cushioned table and rested for five minutes while a brachial blood pressure cuff was positioned around the right arm with the valve positioned distally and rotated towards the medial aspect of the arm. During the PWA measurement, brachial blood pressure measurements were obtained, followed by a 10-second sample of brachial pulse waves captured by the oscillometric cuff. From the brachial measurements, transfer functions are applied to generate a reconstructed aortic pulse waveform (Butlin & Qasem, 2016). From the reconstructed aortic waveform, all measures of aortic systolic (ASBP), diastolic (ADBP), mean (AMAP), and pulse pressures (APP) as well as resting heart rate (HR), ED and SEVR were derived. The ED was defined as beginning with the initial upstroke of the forward wave and ending with the occurrence of the dicrotic notch and was reported as both EDms and ED%. The Buckberg SEVR was determined in the XCEL by the quotient of the diastolic pressure-time area to the systolic pressure-time area. The ratio was then expressed as a percentage, with values higher than 100% indicating that the diastolic pressure-time area was greater than the systolic.

Measures of PWA were performed a minimum of three times with one-minute rest intervals and until at least two tests were within the standard allowable range (± 5 mmHg) for brachial systolic and diastolic pressure (Pickering et al., 2005). Quality of the pulse waveforms of each measurement were evaluated, with the acceptable quality control set at ≥90%. Once determined, the two best trials for each participant were averaged and reported.

Measurement of Pulse Wave Velocity

Measured via applanation tonometry, cf-PWV (m/s) was calculated as the distance between carotid-femoral measurement sites (m) divided by the transit time of the pulse wave (s). Upon completion of the PWA, the participant remained supine while an oscillometric cuff was positioned around the right thigh with the cuff valve positioned proximomedially to the thigh. Three measurements indicative of vascular distance were then made with tape measure (in cm): 1. Carotid artery (located via palpation) to sternal notch, 2. Sternal notch to the proximal end of cuff, 3. Femoral pulse to the proximal end of cuff. Each test was assessed for passing quality by analyzing waveform amplitude and consistency. A minimum of two trials were performed sequentially with additional trials added if values did not fall within the acceptable range of 0.3 m/s (Butlin & Qasem, 2016). The average of the two accepted measures was reported and included in analysis.

Statistical Analysis

The dependent variables obtained from anthropometrics, body composition, PWA and PWV assessments were grouped and analyzed using a one-way ANOVA. Assumptions of sphericity were verified using Levene's test for homogeneity of variance. The Cohen's d measure of effect size was also determined and reported for all measures of PWA and cf-PWV. Analyses were performed using SPSS Software (IBM). A priori level of significance was set at $p \pm 0.05$. Results are expressed as mean ± SD.

Results

Thirty-four sex and age-matched participants were included in this study. Half of the sample (17, 11 male & 6 female) was classified as OW with the other half (11 male & 6 female) classified as NW. Both groups were of similar age and height, while the OW group reported significantly greater weight, BMI, and %FM as expected. The descriptive characteristics of both samples can be seen in Table 1.

All cardiovascular measures along with their respective p-values and effect sizes are reported in table 2. Compared to the NW group, OW adolescents reported significantly higher measures of cf-PWV ($F (1,32) = 6.558$) and ASBP ($F (1,32) = 4.444$) and a significantly lower SEVR ($F (1,32) = 4.663$). Measures of ED, both in milliseconds and relative to the total cardiac cycle, were not significantly different between OW and NW children. Concurrently, resting HR, ADBP, AMAP and APP were not significantly different between groups.

Table 1

Descriptive characteristics of participants. All data are reported mean ± SD.

Descriptive	Normal Weight (N=17)	Overweight (N=17)	*p* value
Age (years)	14.2 ± 2.4	14.1 ± 2.3	1.000
Height (cm)	165.3 ± 12.8	166.6 ± 11.7	0.762
Weight (kg)	51.8 ± 10.4	82.1 ± 23.7	< 0.01
BMI (kg/m^2)	18.8 ± 2.2	29.9 ± 5.4	< 0.01
FM (%)	17.3 ± 8.7	36.1 ± 10.3	< 0.01

Note. BMI, body mass index; FM, fat mass.

Table 2

Cardiovascular measurements of all participants split by groups. Data are reported mean ± SD.

Measurement	Normal Weight (N=17)	Overweight (N = 17)	*p* value	Cohen's d
ASBP (mmHg)	95.7 ± 8.2	103.1 ± 11.8	0.043	0.72
ADBP (mmHg)	62.7 ± 7.1	68.0 ± 10.2	0.086	0.61
AMAP (mmHg)	75.8 ± 7.3	81.9 ± 11.5	0.075	0.63
APP (mmHg)	33.2 ± 5.5	34.8 ± 5.9	0.421	0.28
HR (bpm)	66.8 ± 9.1	73.2 ± 10.5	0.066	0.65
SEVR (%)	132.2 ± 22.0	114.4 ± 25.9	0.038	0.33
ED (%)	38.8 ± 5.4	41.7 ± 5.9	0.151	0.51
ED (ms)	345.9 ± 19.3	345.8 ± 19.0	0.975	0.01
cf-PWV (m/s)	4.5 ± 0.5	5.1 ± 0.9	0.015	0.88

Note. ASBP, aortic systolic blood pressure; ADBP, aortic diastolic blood pressure; AMAP, aortic mean arterial pressure; APP, aortic pulse pressure; HR, resting heart rate; cf-PWV, carotid -femoral pulse wave velocity; SEVR, subendocardial viability ratio; ED(%), relative ejection duration; ED(ms), absolute ejection duration.

Discussion

The purpose of this investigation was to assess if the measurement of ED, SEVR, and other established measures of central arterial health are measurably different in overweight compared to normal weight adolescents. We aimed to explore if measurements of ED and SEVR could lend a meaningful perspective to the prognosis of overweight children regarding their CV health when studied in conjunction with aortic blood pressure and cf-PWV.

The primary finding demonstrated that cf-PWV and ASBP were higher in OW than in NW adolescents (table 2). Measurements of cf-PWV and PWA are accepted as valid measures of arterial stiffness in adults, however, they pose a greater technical challenge in children due to a lack of supporting validation studies and ethical concerns of performing invasive methodologies in healthy young populations (Savant et al., 2014; Urbina et al., 2009). Despite this, many studies in children report a positive association between BMI and cf-PWV (Çelik et al., 2011; Correia-Costa et al., 2016; Dangardt et al., 2013; Sakuragi et al., 2009; Urbina et al., 2010) as well as with ASBP (Castro et al., 2016; García-Espinosa et al., 2016). In a study of 84 children of similar age to our adolescent groups (10-18 years old), obese children reported higher values of PWV and central SBP. Amongst the obese children studied, those who were hypertensive (45 children) reported the highest values of Central SBP, PWV, and left ventricular mass as measured by echocardiography, further suggesting the potential for maladaptive cardiac remodeling in these individuals (Wojtowicz et al., 2017). Our reported increases of cf-PWV and ASBP in OW children are consistent with the existing literature and provide further support of a relationship between the OW condition and the development of stiffer central arteries. This change is recognized as unfavorable, as affected adolescents are likely placed at higher risk for the development of future CVD (Ayer et al., 2015; Cote et al., 2013).

Concurrently, it was found that elevated values of central pressure and stiffness were accompanied by a significant decrease in the SEVR for OW adolescents (table 2); a population for which few studies have investigated the utility of the measurement. In adults, work by Smith and colleagues found that baseline measures of the SEVR were decreased in obese versus nonobese firefighters, indicating that a greater resting myocardial effort exists in the obese individuals and that the SEVR demonstrates clinical value worth further exploration as an indicator of CVD risk (Smith et al., 2012). Our findings concur with those observed in previous work and establish that the relationship between SEVR and excessive adiposity is similar in adolescence as it is in adulthood. We also recognize that SEVR values in OW adolescents are brought down in part by the concomitant increase in ASBP and by a marginal increase in the relative ED. A greater aortic systolic pressure requires an increase in myocardial work and is reflected by the SEVR as a larger systolic AUC. Although myocardial ischemia was not indicated in any of our OW adolescents, the observed changes in SEVR suggest a potential reduction in the myocardial perfusion, which may result in greater myocardial stress. This suggested reduction in perfusion is supported by adult research, which reports a decreased SEVR as an indication of adverse coronary perfusion in obese individuals (Khoshdel & Eshtiaghi, 2019). In a study of hypertensive adults with normal coronary arteries, SEVR was also independently related to a reduction in coronary blood flow reserve, a measure which was also associated with increased left ventricular mass (Tsiachris et al., 2012). Although little work has been performed in adolescent children, the findings of our study in conjunction with the existing body of adult research indicates that the

SEVR may be an important cardiovascular measure in overweight children and should be further evaluated on its utility in adolescent cohorts to predict risk of current and future CVD.

As previously mentioned, measurements of SEVR and the ED in children have not been previously considered in the assessment of present and future CVD risk in children. Our investigation is therefore exploratory in nature, as we consider if these measures may lend another perspective by which the effects of pediatric obesity can be observed. Our results reported no difference in the ED measured in milliseconds between NW and OW participants. These results are unsurprising, since changes in the time of ejection and other systolic time intervals are considerable only in the incidence of severe cardiac remodeling (Weber et al., 2006; Weissler et al., 1968), which is unexpected in our nonclinical population.

Because of the increased metabolic demand associated with the overweight and obese condition (Cote et al., 2013), a decrease in vagal tone leading to greater activity of the sympathetic nervous system has been reported in obese persons (Shibao et al., 2007; Tuck, 1992). Although sympathetic activity was unable to be measured directly in this study, our OW group tended to report higher resting HR values than the NW group, an observation supported by a moderate effect size and a near-significant p-value (table 2). Although our results were unable to achieve statistical significance ($p = 0.066$), previous research has shown significant findings reporting higher resting HR in obese children (Urbina et al., 2010) and a significant relationship between BMI and resting HR in adolescent boys and girls (Baba et al., 2007). When HR data is combined with the observed increases in ASBP in our OW group, the results remain consistent with the effects of elevated sympathetic activity in obese persons (Kalil & Haynes, 2012) suggesting that an elevated sympathetic activity may lead to an increased cardiovascular stress in overweight children. As HR increases, the diastolic time allotted for is subsequently reduced. Because adequate cardiac output must be maintained, and the ejection duration is dependent heavily on stroke volume (Braunwald et al., 1958; Hamada et al., 1990), the EDms remained unchanged in our participants (table 2). It was our hypothesis that in OW adolescents, an increased cardiovascular workload may augment the proportion of the heart rate period spent in systole, and characterizable by an increase in the ED%. The subsequent reduction in diastolic timing may contribute to a reduced capacity for myocardial oxygen supply via the coronary arteries, as detectable by the SEVR, and would indicate a subtle increase in baseline myocardial stress in overweight adolescents. Although ED% results were not statistically significant, the observation of a moderate effect size and higher mean values in the OW group indicate a positive trend in ED% with adiposity. In a study of almost 70 men evaluated for components of metabolic syndrome, significant increases in ED% were reported in subjects with metabolic syndrome with a difference in mean values of 2% and a standard deviation of 3% (Khoshdel & Eshtiaghi, 2019). Our findings in adolescents report an almost 3% difference in mean values of ED% with a 5% standard deviation in a much smaller sample, suggesting that significance may be achieved in a larger more robust sample. An a-priori power calculation based on the obtained results determined that a sample of 57 OW adolescents (n=117) would provide adequate statistical power (power = 0.85) for the measurement of ED%. The attainment of this larger sample remains feasible and justifies the continuation of this line of research.

The present study demonstrates limitations that future studies should work to address. Although participants were matched between groups on the basis of sex and age, the comparison groups ultimately were not separated by sex. Also, the menstrual cycle in females was not controlled for despite having potential effects on the systolic function (Ounis-Skali et al., 2006). As previously outlined, our study is limited by a small sample of OW participants in which few adolescents were identified as obese. Given that obesity severity is identified as an important factor in the evaluation of CVD risk (Freedman et al., 2007), future works should emphasize the recruitment of more severely obese individuals in order to better elucidate the capability of non-invasive cardiovascular measures to detect change.

This observational study explored the utility of the ejection duration, subendocardial viability ratio, and several other subclinical measures in the assessment of cardiovascular health in a previously unresearched sample of OW and NW children. In support of our second hypothesis, measures of pulse wave velocity, aortic systolic blood pressure, and SEVR were all negatively affected by the overweight condition in adolescents, indicating that these parameters demonstrate utility in the detection of cardiovascular change. Further investigation of these measures is warranted to determine the extent of their clinical value in this cohort. In contrast to our first hypothesis, the ED% was not found significantly increased in our overweight group. Despite this, the observations of a higher mean value in overweight children and a moderate effect size indicate that the ED% may still lend to the assessment of CVD risk. For a better discernment of prognostic worth, a larger sample with more obese adolescents is warranted. Overall, the findings of this study qualify the continuation of this research, so that we may better understand the preventative nature of these non-invasive cardiovascular measurements in adolescent cohorts.

References

Aslanger, E., Assous, B., Bihry, N., Beauvais, F., Logeart, D., & Cohen-Solal, A. (2017). Baseline subendocardial viability ratio influences left ventricular systolic improvement with cardiac rehabilitation. *Anatolian Journal of Cardiology, 17*(1), 37.

Ayer, J., Charakida, M., Deanfield, J. E., & Celermajer, D. S. (2015). Lifetime risk: childhood obesity and cardiovascular risk. *European heart journal, 36*(22), 1371-1376.

Baba, R., Koketsu, M., Nagashima, M., Inasaka, H., Yoshinaga, M., & Yokota, M. (2007). Adolescent obesity adversely affects blood pressure and resting heart rate. *Circulation Journal, 71*(5), 722-726.

Biering-Sørensen, T., Querejeta Roca, G., Hegde, S. M., Shah, A. M., Claggett, B., Mosley Jr, T. H., Butler Jr, K. R., & Solomon, S. D. (2018). Left ventricular ejection time is an independent predictor of incident heart failure in a community-based cohort. *European journal of heart failure, 20*(7), 1106-1114.

Brady, T. M. (2017). Obesity-related hypertension in children. *Frontiers in pediatrics, 5*, 197.

Brady, T. M., Fivush, B., Flynn, J. T., & Parekh, R. (2008). Ability of blood pressure to predict left ventricular hypertrophy in children with primary hypertension. *The Journal of pediatrics, 152*(1), 73-78. e71. https://www.jpeds.com/article/S0022-3476(07)00558-6/fulltext

Braunwald, E., Sarnoff, S., & Stainsby, W. (1958). Determinants of duration and mean rate of ventricular ejection. *Circulation research, 6*(3), 319-325.

Brown, C. D., Higgins, M., Donato, K. A., Rohde, F. C., Garrison, R., Obarzanek, E., Ernst, N. D., & Horan, M. (2000). Body mass index and the prevalence of hypertension and dyslipidemia. *Obesity research, 8*(9), 605-619.

Buckberg, G. D., Fixler, D. E., Archie, J. P., & Hoffman, J. I. (1972). Experimental subendocardial ischemia in dogs with normal coronary arteries. *Circulation research, 30*(1), 67-81.

Butlin, M., & Qasem, A. (2016). Large artery stiffness assessment using SphygmoCor technology. *Pulse, 4*(4), 180-192.

Castro, J. M., García-Espinosa, V., Curcio, S., Arana, M., Chiesa, P., Giachetto, G., Zócalo, Y., & Bia, D. (2016). Childhood obesity associates haemodynamic and vascular changes that result in increased central aortic pressure with augmented incident and reflected wave components, without changes in peripheral amplification. *International Journal of Vascular Medicine, 2016*.

Çelik, A., Özçetin, M., Yerli, Y., Damar, İ. H., Kadı, H., Koç, F., & Ceyhan, K. (2011). Increased aortic pulse wave velocity in obese children. *Archives of the Turkish Society of Cardiology, 39*(7), 557-562.

Correia-Costa, A., Correia-Costa, L., Afonso, A. C., Schaefer, F., Guerra, A., Moura, C., Mota, C., Barros, H., Areias, J. C., & Azevedo, A. (2016). Determinants of carotid-femoral pulse wave velocity in prepubertal children. *International journal of cardiology, 218*, 37-42.

Cote, A. T., Harris, K. C., Panagiotopoulos, C., Sandor, G. G., & Devlin, A. M. (2013). Childhood Obesity and CardiovascularáDysfunction. *Journal of the American College of Cardiology, 62*(15), 1309-1319.

Dangardt, F., Chen, Y., Berggren, K., Osika, W., & Friberg, P. (2013). Increased rate of arterial stiffening with obesity in adolescents: a five-year follow-up study. *PloS one, 8*(2), e57454.

Ewald, D. R., & Haldeman, L. A. (2016). Risk factors in adolescent hypertension. *Global Pediatric Health, 3*, 2333794X15625159.

Freedman, D. S., Mei, Z., Srinivasan, S. R., Berenson, G. S., & Dietz, W. H. (2007). Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. *The Journal of pediatrics, 150*(1), 12-17. e12.

García-Espinosa, V., Curcio, S., Castro, J. M., Arana, M., Giachetto, G., Chiesa, P., Zócalo, Y., & Bia, D. (2016). Children and adolescent obesity associates with pressure-dependent and age-related increase in carotid and femoral arteries' stiffness and not in brachial artery, indicative of nonintrinsic arterial wall alteration. *International Journal of Vascular Medicine, 2016*.

Garrard Jr, C. L., Weissler, A. M., & Dodge, H. T. (1970). The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation, 42*(3), 455-462.

Haiden, A., Eber, B., & Weber, T. (2014). U-shaped relationship of left ventricular ejection time index and all-cause mortality. *American journal of hypertension, 27*(5), 702-709.

Hales, C. M., Carroll, M. D., Fryar, C. D., & Ogden, C. L. (2017). Prevalence of obesity among adults and youth: United States, 2015–2016.

Hamada, M., Hiwada, K., & Kokubu, T. (1990). Clinical significance of systolic time intervals in hypertensive patients. *European heart journal, 11*(suppl_I), 105-113.

Hassan, S., & Turner, P. (1983). Systolic time intervals: a review of the method in the non-invasive investigation of cardiac function in health, disease and clinical pharmacology. *Postgraduate Medical Journal, 59*(693), 423-434.

Hubert, H. B., Feinleib, M., McNamara, P. M., & Castelli, W. P. (1983). Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation, 67*(5), 968-977.

Kalil, G. Z., & Haynes, W. G. (2012). Sympathetic nervous system in obesity-related hypertension: mechanisms and clinical implications. *Hypertension Research, 35*(1), 4-16.

Khoshdel, A. R., & Eshtiaghi, R. (2019). Assessment of arterial stiffness in metabolic syndrome related to insulin resistance in apparently healthy men. *Metabolic syndrome and related disorders, 17*(2), 90-96.

Le, J., Zhang, D., Menees, S., Chen, J., & Raghuveer, G. (2010). "Vascular age" is advanced in children with atherosclerosis-promoting risk factors. *Circulation: Cardiovascular Imaging, 3*(1), 8-14.

Lewis, R. P., Rittogers, S., Froester, W., & Boudoulas, H. (1977). A critical review of the systolic time intervals. *Circulation, 56*(2), 146-158.

Lobstein, T., Baur, L., Uauy, R., & TaskForce, I. I. O. (2004, May). Obesity in children and young people: a crisis in public health. *Obes Rev, 5 Suppl 1*, 4-104. https://doi.org/10.1111/j.1467-789X.2004.00133.x

Masuo, K., Mikami, H., Ogihara, T., & Tuck, M. L. (2000). Weight gain–induced blood pressure elevation. *Hypertension, 35*(5), 1135-1140.

Must, A., & Strauss, R. S. (1999). Risks and consequences of childhood and adolescent obesity. *International journal of obesity, 23*(2), S2-S11.

Obata, Y., Mizogami, M., Singh, S., Nyhan, D., Berkowitz, D. E., Steppan, J., & Barodka, V. (2017). Ejection time: influence of hemodynamics and site of measurement in the arterial tree. *Hypertension Research, 40*(9), 811-818.

Olshansky, S. J., Passaro, D. J., Hershow, R. C., Layden, J., Carnes, B. A., Brody, J., Hayflick, L., Butler, R. N., Allison, D. B., & Ludwig, D. S. (2005, Mar 17). A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med, 352*(11), 1138-1145. https://doi.org/10.1056/NEJMsr043743

Ounis-Skali, N., Mitchell, G. F., Solomon, C. G., Solomon, S. D., & Seely, E. W. (2006). Changes in central arterial pressure waveforms during the normal menstrual cycle. *Journal of investigative medicine, 54*(6), 321-326.

Parker, E. D., Sinaiko, A. R., Kharbanda, E. O., Margolis, K. L., Daley, M. F., Trower, N. K., Sherwood, N. E., Greenspan, L. C., Lo, J. C., & Magid, D. J. (2016). Change in weight status and development of hypertension. *Pediatrics, 137*(3), e20151662.

Pickering, T. G., Hall, J. E., Appel, L. J., Falkner, B. E., Graves, J., Hill, M. N., Jones, D. W., Kurtz, T., Sheps, S. G., & Roccella, E. J. (2005). Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension, 45*(1), 142-161.

Sakuragi, S., Abhayaratna, K., Gravenmaker, K. J., O'Reilly, C., Srikusalanukul, W., Budge, M. M., Telford, R. D., & Abhayaratna, W. P. (2009). Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. *Hypertension, 53*(4), 611-616.

Salvi, P., Revera, M., Faini, A., Giuliano, A., Gregorini, F., Agostoni, P., Becerra, C. G. R., Bilo, G., Lombardi, C., & O'Rourke, M. F. (2013). Changes in subendocardial viability ratio with acute high-altitude exposure and protective role of acetazolamide. *Hypertension, 61*(4), 793-799.

Savant, J. D., Furth, S. L., & Meyers, K. E. (2014). Arterial stiffness in children: pediatric measurement and considerations. *Pulse, 2*(1-4), 69-80.

Scandale, G., Dimitrov, G., Recchia, M., Carzaniga, G., Minola, M., Perilli, E., Carotta, M., & Catalano, M. (2018). Arterial stiffness and subendocardial viability ratio in patients with peripheral arterial disease. *The Journal of Clinical Hypertension, 20*(3), 478-484.

Shibao, C., Gamboa, A., Diedrich, A., Ertl, A. C., Chen, K. Y., Byrne, D. W., Farley, G., Paranjape, S. Y., Davis, S. N., & Biaggioni, I. (2007). Autonomic contribution to blood pressure and metabolism in obesity. *Hypertension, 49*(1), 27-33.

Smith, D. L., Fehling, P. C., Frisch, A., Haller, J. M., Winke, M., & Dailey, M. W. (2012). The prevalence of cardiovascular disease risk factors and obesity in firefighters. *Journal of obesity, 2012*.

Tounian, P., Aggoun, Y., Dubern, B., Varille, V., Guy-Grand, B., Sidi, D., Girardet, J.-P., & Bonnet, D. (2001). Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *The Lancet, 358*(9291), 1400-1404.

Tsiachris, D., Tsioufis, C., Syrseloudis, D., Roussos, D., Tatsis, I., Dimitriadis, K., Toutouzas, K., Tsiamis, E., & Stefanadis, C. (2012). Subendocardial viability ratio as an index of impaired coronary flow reserve in hypertensives without significant coronary artery stenoses. *Journal of human hypertension, 26*(1), 64-70.

Tu, W., Eckert, G. J., DiMeglio, L. A., Yu, Z., Jung, J., & Pratt, J. H. (2011). Intensified effect of adiposity on blood pressure in overweight and obese children. *Hypertension, 58*(5), 818-824.

Tuck, M. (1992). Obesity, the sympathetic nervous system, and essential hypertension. *Hypertension, 19*(1_supplement), I67.

Urbina, E. M., Kimball, T. R., Khoury, P. R., Daniels, S. R., & Dolan, L. M. (2010). Increased arterial stiffness is found in adolescents with obesity or obesity-related type 2 diabetes mellitus. *Journal of hypertension, 28*(8), 1692.

Urbina, E. M., Williams, R. V., Alpert, B. S., Collins, R. T., Daniels, S. R., Hayman, L., Jacobson, M., Mahoney, L., Mietus-Snyder, M., & Rocchini, A. (2009). Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. *Hypertension, 54*(5), 919-950.

Weber, T., Auer, J., O'Rourke, M. F., Punzengruber, C., Kvas, E., & Eber, B. (2006). Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction. *Heart, 92*(11), 1616-1622.

Weissler, A. M., Harris, W. S., & Schoenfeld, C. D. (1968). Systolic time intervals in heart failure in man. *Circulation, 37*(2), 149-159.

Wojtowicz, J., Łempicka, A., Łuczyński, W., Szczepański, W., Zomerfeld, A., Semeran, K., & Bossowski, A. (2017). Central aortic pressure, arterial stiffness and echocardiographic parameters of children with overweight/obesity and arterial hypertension. *Advances in clinical and experimental medicine: official organ Wroclaw Medical University, 26*(9), 1399-1404.

Xi, B., Zhang, T., Li, S., Harville, E., Bazzano, L., He, J., & Chen, W. (2017). Can pediatric hypertension criteria be simplified? A prediction analysis of subclinical cardiovascular outcomes from the Bogalusa Heart Study. *Hypertension, 69*(4), 691-696.

Vita

Nicholas Tocci was born in Durham, North Carolina, to his mother Lynn and father Doug Tocci. He graduated from Chapel Hill High School in Chapel Hill, NC, in June of 2015, and the following August, began his undergraduate career at Appalachian State University majoring in Exercise Science. Upon graduating in May of 2019, he immediately enrolled as a graduate student in Exercise Science via accelerated admission and obtained part-time graduate assistantship positions under Dr. Meucci in the Pediatric Exercise Physiology Laboratory and under Dr. Anne Moody in cardiopulmonary rehabilitation while working towards his graduate degree. Nicholas will be graduating with a Master of Science in Exercise Science with a concentration in clinical exercise physiology in August of 2020.