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Racial Differences in Aortic Stiffness in Children

Wesley K Lefferts, MS¹, Jacqueline A Augustine, MS¹, Nicole L Spartano, PhD¹, Nader H Atallah-Yunes, MD², Kevin S Heffernan, PhD¹, and Brooks B Gump, PhD³

¹Department of Exercise Science, Syracuse University

²Pediatric Cardiology, Upstate Medical University

³Department of Public Health, Syracuse University

Abstract

Objective—To investigate racial differences in central blood pressure and vascular structure/function as subclinical markers of atherosclerotic cardiovascular disease (CVD) in children.

Study design—This cross-sectional study recruited 54 African-American children (18 female, 36 male; age 10.5 ± 0.9) and 54 white children (27 female, 26 male; age 10.8 ± 0.9) from the Syracuse City community as part of the Environmental Exposures and Child Health Outcomes (EECHO) study. Participants underwent blood lipid and vascular testing on two separate days. Carotid artery intima-media thickness (IMT) and aortic stiffness were measured via ultrasonography and carotid-femoral pulse wave velocity (PWV), respectively. Blood pressure (BP) was assessed at the brachial artery and estimated in the carotid artery using applanation tonometry.

Results—African American children had significantly higher PWV (4.8 ± 0.8 m/s) compared with white children (4.2 ± 0.7 m/s; $p < 0.05$) which remained significant after adjustment for confounding variables including socioeconomic status. African-American children had significantly higher IMT (African-American 0.41 ± 0.06 , white 0.39 ± 0.05 mm), and carotid systolic BP (African-American 106 ± 11 , white 102 ± 8 mmHg; $p < 0.05$) compared with white children, although these racial differences were no longer present after covariate adjustments for height.

Conclusions—Racial differences in aortic stiffness are present in childhood. Our findings suggest that racial differences in subclinical CVD occur earlier than previously recognized.

Keywords

pediatrics; race; arterial stiffness; central blood pressure

Corresponding Author: Kevin S. Heffernan, PhD, The Human Performance Laboratory, Department of Exercise Science, Syracuse University, Syracuse NY, 13244, USA, Phone: 315-443-9801, Fax: 315-443-9375, ksheffer@syr.edu.

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Cardiovascular disease (CVD) morbidity and mortality is greater in African Americans compared with their white American counterparts.¹ African Americans appear to develop elevated blood pressure (BP)² and related sequela like heart failure³ earlier in life compared with white Americans and racial differences in BP have been documented in young adults.⁴ Racial differences in the prevalence of elevated BP and overall hemodynamic burden in children has not been consistently noted^{5, 6} and this may be related to the manner in which hemodynamic load is assessed.

BP is traditionally measured in the brachial artery, but this may not accurately mirror load placed on the central vasculature and heart.⁷ Methods have been devised to noninvasively estimate central BP which holds greater prognostic capability than conventional BP; central BP is more predictive of vascular target organ damage, cardiovascular morbidity and cardiovascular mortality than brachial BP among adults.^{7, 8} Assessment of central BP may be particularly useful for the assessment of CVD risk in African Americans^{9, 10} as young African Americans may have higher central BP compared with white Americans despite comparable brachial BP.^{11, 15} Racial differences in central BP may be the result of early vascular aging among African Americans.^{11, 15} Large (central) artery stiffness increases with advancing age owing to numerous structural and functional changes.¹² Young and middle-aged African-American adults have higher aortic stiffness than their age-matched white counterparts.^{4, 13, 14} These racial differences in aortic stiffness are important to note because aortic stiffness is a predictor of CVD risk later in life^{15, 16} and is associated with hypertensive target organ damage in African Americans.¹⁷

The purpose of this study was to investigate racial differences in central hemodynamic burden and vascular structure/function as subclinical markers of atherosclerotic CVD in children. The first specific aim was to investigate racial differences in central BP among African-American children and white children. It was hypothesized that African-American children would exhibit higher central BP compared with their white counterparts. The second specific aim was to explore racial differences in aortic stiffness and carotid intima media thickness (IMT) as measures of early vascular aging and vascular target organ damage.^{18, 19} We hypothesized that aortic stiffness and carotid IMT would be higher in African-American children compared with white children.

Methods

108 children (54 African American [18 female], 53 white [27 female]) from the Syracuse City community participated in this study as part of the Environmental Exposures and Child Health Outcomes (EECHO) study, a larger, ongoing investigation. Descriptive characteristics are displayed in Table I. Participants' race was identified by parents as African-American or white. All participants were English speaking, between 9-12 years of age, had a body mass >18kg, and were free from any serious medical/developmental disabilities that would prevent them from participating in the study, as assessed by a health history questionnaire filled out by the guardian. Participants had no medical history of cancer, diagnosed hypertension, stroke, thyroid disease, pancreatitis, neuralgia, or diabetes. Medication use in our cohort included drugs for asthma (n=30), respiratory allergies (n=17), and attention-deficit/attention-deficit-hyperactivity disorder (ADD/ADHD; n=8). This study

was approved by the institutional review board of Syracuse University and SUNY Upstate University. All guardians and participants gave written consent and assent, respectively, prior to enrollment.

All participants underwent testing on two separate days (day 1, fasted blood lipids; day 2, descriptive measures and vascular assessment). Visits were separated by approximately 2 weeks. All visits occurred between 8:00AM and 12:00PM. Participants were instructed to arrive in a fasted state and avoid taking vasoactive medications (ie, medication for respiratory allergies, attention-deficit disorder) on test days. Vascular measures were assessed in the supine position following a 5-minute supine rest period in a dimly-lit, temperature-controlled laboratory.

Total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TRG) and glucose levels (GLU) were measured from venous blood using an automated point-of-care blood lipid analysis device (Cholestech LDX). Participants were classified as having dyslipidemia according to the guidelines established by the Expert Panel on Cardiovascular Health and Risk Reduction in Children and Adolescents.²⁰

Height and weight were assessed using a mechanical physician scale and stadiometer (Detecto, Webb City, MO). Body mass index (BMI) was calculated as weight (kg)/height (m)². Socioeconomic status (SES) score was calculated based on parental occupation, income, and education data. Level of parental education and parental occupation were scored using a 1-7 scale and 1-9 scale, respectively.²¹ Parental income was based on a 1-10 scale and adjusted by dividing income by the square root of the number of people living in the household.²² Occupation, income, and data from each of these three indices were averaged across parents for each participant when data from both parents was available. All income, education, and occupation data were finally converted into a z-score. Participants also reported subjective pubertal development using Peterson's Pubertal Development Scale²³ (scale from 1-5; 1 = pre-pubertal, 2 = early puberty, 3 = mid-puberty, 4 = late puberty, 5 = post-pubertal).

The common carotid artery was imaged below the carotid bulb using ultrasound (ProSound α7, Aloka, Tokyo, Japan) and a 7.5-10.0 MHz linear-array probe. Common carotid artery intima-media thickness (IMT) was assessed using a longitudinal view of the artery with both near wall and far wall lumen-IMT boundaries clearly visible. IMT was measured as the distance from the lumen-intima interface to the media-adventitia interface across a 5 mm region of interest via semi-automated digital calipers during diastole (indicated by the R-wave from simultaneous ECG gating).

Applanation tonometry (AtCor Medical, Sydney, Australia) was used to acquire pressure waves at two sites on the right side of the body (carotid- femoral). The distances from the suprasternal notch to the femoral and carotid arteries were measured using a standard tape measure to the nearest mm. Consistent waveforms were collected over 10 s from the carotid and femoral arteries using a high-fidelity tonometer. Carotid-femoral PWV was calculated using the distance (femoral – carotid, to account for different directions of pressure wave

transmission) and the measured time delay between the proximal/distal waveforms and peak R wave from simultaneous ECG gating and taken as a measure of aortic stiffness.

Brachial systolic BP (SBP), diastolic brachial BP (DBP), and mean arterial pressure (MAP) were measured on the non-dominant arm using a validated, automated oscillometric sphygmomanometer (Mobil-O-Graph, I.E.M.).²⁴ Pressures were taken in duplicate and averaged. If values were different by more than 5 mmHg, a third measure was obtained and the average of the 2 closest measures was used for subsequent analyses. Carotid pressure waveforms obtained during the measurement of PWV (described above) were ensemble averaged to a single waveform for determination of carotid SBP. Carotid waveforms were calibrated to brachial MAP and DBP. Mean arterial pressure (MAP) and pulse pressure (PP) were calculated as $1/3 \text{ SBP} + 2/3 \text{ DBP}$ and $\text{SBP} - \text{DBP}$, respectively. Resting brachial BP values were categorized as hypertensive if they were 95th percentile for height, in accordance with pediatric hypertension guidelines.²⁵

Statistical Analyses

All data are reported as mean $\pm$ standard deviation. A chi-square test was used to test differences in sex distribution between groups. The effect of race on descriptive and vascular measures were assessed using analysis of variance. Analysis of covariance was used to test the effect of race on continuous outcome variables after adjusting for potential confounding variables. All main vascular outcome variables were adjusted for covariates in a two-step model. The first covariates entered into the model were age, sex, BMI, MAP, and SES. The second step entered height into the model as a covariate in order to account for differences in growth, as is common in research using children. A similar process was followed for central and peripheral BP. Step 1 included adjustments for age, sex, BMI, and SES, and step 2 included the addition of height. Although collinearity is a concern when entering BMI and height in the same model, each captures a unique effect that may likely impact vascular structure/function: obesity (BMI), and growth (height). Correlations of interest were investigated using Pearson correlation coefficients for the total sample. All analyses were performed using Statistical Package for the Social Sciences (SPSS, version 23, Chicago, IL) with significance set *a priori* as $p < 0.05$.

Results

Groups were similar in age and sex (Table I). Although African-American participants were significantly taller and heavier than white participants, racial differences in BMI did not achieve significance ($p > 0.05$). Socioeconomic status, expressed as a z-score, indicated African-American participants had significantly lower SES compared with white participants ($p < 0.05$). There were no racial differences in subjective pubertal development, fasted blood lipids (cholesterol, HDL, triglycerides), glucose levels, or prevalence of hypertension, dyslipidemia, asthma, or ADD/ADHD ($p > 0.05$).

Vascular Structure and Function

Significant racial differences were noted in both carotid IMT and aortic PWV (Table II). African-American children had significantly higher carotid IMT and aortic PWV compared

with white children ($p < 0.05$). Racial differences remained significant after step 1 adjustments for age, sex, BMI, MAP, and SES. Racial differences in carotid IMT were no longer present following adjustment for height in step 2 (adjusted IMT means: African-American 0.41 ± 0.06 ; white 0.39 ± 0.06 mm, $p = 0.203$). Racial differences in PWV remained following multi-variable adjustment including height (Adjusted PWV means: African-American 4.7 ± 0.8 ; white 4.2 ± 0.8 m/s, $p = 0.006$).

Peripheral and Central Blood Pressure

There were no racial differences in brachial SBP ($p > 0.05$). African-American children had significantly greater brachial DBP and carotid SBP compared with white children ($p < 0.05$; Table II). Brachial DBP and carotid SBP remained significant after step 1 adjustments for age, sex, BMI and SES. Racial differences in carotid SBP were no longer present after further adjusting for height in step 2 (adjusted carotid SBP means: African-American 105 ± 10 ; White 102 ± 10 mmHg, $p = 0.165$).

Pearson product correlation coefficients for select vascular measures in all participants are presented in Table III. BMI was associated with IMT, PWV, and central SBP ($p < 0.05$). Height was associated with BMI, IMT, PWV, and brachial SBP. SES was not associated with any vascularhemodynamic measure ($p > 0.05$).

Discussion

Racial differences in PWV, but not IMT or central systolic pressure, persisted after statistical adjustment for potential confounders (ie, age, sex, MAP, BMI, SES, and height). Carotid-femoral PWV is considered the “gold standard” measure of aortic stiffness¹² and a marker of early vascular aging.¹¹ Data indicate that arterial stiffness increases from as early as 2.3 years of age into adolescence, with the largest changes occurring between 3-7 years of age.¹² In adults, aortic stiffness has been shown to precede the development of hypertension, contribute to target organ damage and increase risk for CVD events (myocardial infarction and stroke).^{15, 16, 26} Previous studies have noted racial differences in aortic stiffness in young, apparently healthy adults with young African-Americans (mean age 23 years) having higher PWV than their white peers.¹³ Although our findings are similar to previous observations in young adults, we observed racial differences in PWV nearly a decade earlier in life than previously recognized. The clinical relevance of these differences has yet to be identified in children however data in adults indicate a 1 m/s increase in PWV confers a 15% increase in CVD risk.²⁶

African-American children had significantly higher central BP, but similar brachial BP, compared with white children. Racial differences in central BP were no longer present after covariate adjustment for potential confounders. Central pressures are a better predictor of target organ damage and risk of future cardiovascular events than brachial pressures in adults.^{8, 27} In younger populations where peripheral systolic pressures tend to overestimate central systolic pressure due to pressure amplification,²⁸ measurement of central pressures may provide more relevant insight into the load experienced by the heart.²⁹ Thus, assessment of brachial pressures alone may neglect important information on central hemodynamic burden in young African-American children. According to our data, however,

central BP proved no more sensitive than brachial BP in identifying racial differences in central hemodynamic burden in children after covariate adjustments. Thus, at least in this age range, racial differences in central BP appear to be related to differences in underlying covariates, namely height.

African-American children had significantly higher IMT compared with their white counterparts, however these racial differences were no longer present following covariate adjustment, specifically height. IMT is a measure of vascular target organ damage and subclinical atherosclerosis,³⁰ and a prospective predictor of CVD events in adults.³¹ Among adolescents, IMT has been associated with cardiovascular health status^{32, 33} and CVD risk factors (obesity/diabetes).³⁴ Moreover, previous studies have shown that African-American adolescents have higher IMT compared with their white counterparts.¹⁴ Although the atherosclerotic process may alter arterial stiffness (by modifying the mechanical function of the artery wall), arterial stiffening is a process distinct from atherosclerosis.³⁵ Thus, it is not surprising that IMT and PWV were not associated within our sample and racial differences in PWV occurred in the absence of differences in IMT. It is possible that akin to what is seen in adults, changes in aortic stiffness precede changes in BP,³⁶ with increases in aortic stiffness and subsequent augmentation of BP contributing to further detrimental vascular remodeling manifesting as increase in vessel size (diameter) and thickness later in life.¹³ Longitudinal studies will be needed to examine whether changes in vessel wall stiffness precede or occur concomitant with changes in vessel wall thickness and whether elevated PWV in childhood tracks into adulthood.

IMT and aortic stiffness in adulthood has been shown to be partially predicted by standard CVD risk factors in childhood (metabolic syndrome,³⁷ physical activity, diet,³⁸ smoking).³⁹ Moreover, in childhood, increased IMT and aortic stiffness has been partially related to increased traditional CVD risk factor burden,^{34, 40} as well as increased body mass index (BMI)⁴¹ and lower socio-economic status (SES).¹⁴ Obesity in early childhood, as commonly assessed using BMI, is used as a tool to identify high-risk individuals. Higher BMI in childhood is typically associated with the presence of more cardio-metabolic risk factors,⁴² high BP/hypertension,⁴³ increased aortic stiffness⁴⁴ and target organ damage.⁴⁵ In the current study there was a trend for African-American children to have greater BMI compared with white children. Moreover, we noted significant associations between BMI and BP, IMT, and PWV, consistent with previous reports.⁴³⁻⁴⁵ Contrastingly, some studies have noted inverse associations between BMI and global-measures of artery stiffness among 10-18 year olds. Philip et al suggested that reduced stiffness among those with higher BMI may not have been indicative of health status, but rather that structural vascular adaptations (ie, greater vasodilation) accompany obesity and may temporarily reduce artery stiffness.⁴⁶ Reasons for these conflicting findings could be due to the larger age range included by Philip et al or differing methodology. Philip et al used the cardio-ankle vascular index, a global measure of artery stiffness which includes peripheral muscular artery stiffness, whereas we utilized aortic PWV which predominantly reflects central elastic artery properties.^{12, 47} Our results support that BMI is an important correlate of subclinical atherosclerotic CVD in children.

SES has been hypothesized as a factor contributing to racial disparities in adult CVD considering the overrepresentation of African-American families in low SES positions.⁴⁸ The influence of low SES on CVD risk likely results from a cumulative exposure to adverse conditions over the lifespan and may impact CVD risk even in early in life.⁴⁹ In line with previous observations,¹⁴ African-American children in our study had significantly lower SES compared with their white counterparts. Previous research by Thurston et al suggested that racial differences in subclinical markers of CVD risk (IMT, PWV) were significantly related to SES in adolescents (approximately 17 years old).¹⁴ Racial differences in both IMT and aortic stiffness observed herein remained significant following covariate adjustment for established confounders (sex, age, BMI, brachial MAP, and SES) suggesting that other factors may mediate/moderate racial differences in vascular structure and function in young children. It is possible that the effect of overweight/obesity and SES on CVD burden may become more prominent with further exposure/increasing age.

Growth is associated with vascular hemodynamics. In the current study, covariate adjustment for height removed racial differences in both IMT and carotid systolic pressure. Thus the greater IMT and carotid systolic pressure observed in African-American children compared with white children appear partially due to African-American children being slightly taller. Previous investigations have identified associations between height and CVD risk,⁵⁰ blood pressure,⁵¹ and IMT⁵² in children. Racial differences in PWV, however, were unaffected by covariate adjustment for height, likely because height is already partially accounted for in the PWV calculation in the form of carotid-femoral path length. Racial differences in height were not accompanied by racial differences in maturation in our sample, highlighting the importance of growth itself. Consistent with our findings, previous data have also shown racial differences in blood pressure are related to differences in height more so than maturation.⁵¹ Taken together and findings indicate an independent role for growth in influencing racial differences in central blood pressure and vascular target organ damage in children.

The mechanisms responsible for the development of racial differences in vascular structure/function are complex and currently unknown. A substantial body of literature, however, has focused on the cardiovascular reactivity to physical (cold-pressor test, exercise) and psychological (speech, arithmetic, video games) stressors as the potential substrate for detrimental vascular remodeling and target-organ damage. Indeed, cardiovascular reactivity is associated with the development of hypertension⁵³ and carotid atherosclerosis (assessed as IMT) in adults,⁵⁴ adolescents,⁵⁵ and children.⁵⁶ Moreover, racial differences in cardiovascular reactivity have been noted.⁵⁷ Data suggest African-American youth have greater BP reactivity compared with their white counterparts.⁵⁸⁻⁶⁰ Racial differences in BP reactivity may be related to greater vasoconstrictor sensitivity among African-Americans, whereby increases in peripheral vascular resistance elevate BP, rather than increases in cardiac inotropy/chronotropy.^{59, 61, 62} Whether racial differences in aortic stiffness contribute to cardiovascular reactivity, or vice versa, has yet to be established. Thus, investigating the relationships between the racial differences in aortic stiffness, cardiovascular reactivity, and the accumulation of CVD risk factors represents a potentially insightful line of future work.

Interpretation of our data may be affected by our modest sample size. As such, it is possible that racial differences in height may not exist in larger samples, or that differences in markers of subclinical CVD may solely stem from racial differences in maturation. Additionally, our study is cross-sectional in nature and relies on non-invasive, subclinical measures of CVD and target organ damage. The measures used herein, however, are widely recommended to assess subclinical atherosclerotic CVD and are used in pediatric and adult populations.^{12, 47} Future studies are necessary to identify the clinical relevance of increased aortic stiffness in children and long-term CVD risk.

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Glossary

Abbreviations and acronyms

Acronym	Definition
CVD	Cardiovascular disease
IMT	Intima-media thickness
BP	Blood pressure
TC	Total cholesterol
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
TRG	Triglycerides
GLU	Glucose
BMI	Body mass index
SES	Socioeconomic status
PWV	Pulse wave velocity
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
PP	Pulse pressure

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Table 1Participant characteristics (mean $\pm$ SD)

	African-American (n=54)	White (n=53)
Age (yrs)	10.5 $\pm$ 0.9	10.8 $\pm$ 0.9
Male n (%)	36 (67)	26 (48)
Female n (%)	18 (33)	27 (52)
Hypertension n (%)	14 (26)	11 (21)
Dyslipidemia n (%)	5 (9)	9 (17)
Asthma n (%)	18 (33)	12 (23)
ADD/ADHD n (%)	8 (15)	5 (9)
Height (cm) *	148 $\pm$ 8	144 $\pm$ 9
Weight (kg) *	49 $\pm$ 16	42 $\pm$ 12
BMI (kg/m ²)	22.1 $\pm$ 5.6	20.1 $\pm$ 5.2
Pubertal Development	2.65 $\pm$ 0.89	2.47 $\pm$ 0.82
Z-score SES *	-0.26 $\pm$ 0.69	0.35 $\pm$ 0.86
Total cholesterol (mg/dl)	153 $\pm$ 23	159 $\pm$ 25
HDL cholesterol (mg/dl)	56 $\pm$ 13	54 $\pm$ 14
Triglycerides (mg/dl)	64 $\pm$ 27	74 $\pm$ 39
Glucose (mg/dl)	91 $\pm$ 7	90 $\pm$ 6

SES, socioeconomic status; HDL, high-density lipoprotein.

* Significant group difference (p<0.05)

Table 2Peripheral and central hemodynamics between races (mean $\pm$ SD)

Variable		African-American (n=54)	White (n=53)
Brachial	Systolic pressure (mmHg)	116 $\pm$ 10	113 $\pm$ 8
	Diastolic pressure (mmHg) *	69 $\pm$ 6	66 $\pm$ 6
	Pulse pressure (mmHg)	47 $\pm$ 9	47 $\pm$ 7
	Mean pressure (mmHg)	84 $\pm$ 7	82 $\pm$ 6
Carotid	Intima-media thickness (mm) *	0.41 $\pm$ 0.06	0.39 $\pm$ 0.05
	Systolic pressure (mmHg) *	106 $\pm$ 11	102 $\pm$ 8
	Pulse pressure (mmHg)	37 $\pm$ 9	36 $\pm$ 8
Aortic	Pulse wave velocity (m/s) *	4.8 $\pm$ 0.8	4.2 $\pm$ 0.7
	Heart rate (bpm) *	77 $\pm$ 11	71 $\pm$ 7

* Significant group difference (p<0.05)

Table 3

Pearson correlation coefficients for select vascular measures among all children (n = 107)

Variable	BMI	SES	Height	IMT	PWV	SBP _{brachial}
SES	0.031					
Height	0.292 [*]	−0.044				
IMT	0.256 [*]	−0.036	0.373 [*]			
PWV	0.226 [*]	−0.107	0.199 [*]	−0.046		
SBP _{brachial}	0.275 [*]	0.075	0.313 [*]	0.069	0.241 [*]	
SBP _{carotid}	0.352 [*]	0.040	0.171	0.149	0.215 [*]	0.870 [*]

SES, Z-score socioeconomic status; IMT, intima-media thickness; PWV, pulse wave velocity; SBP, systolic blood pressure.

^{*} p < 0.05