Associations of cardiac structure with obesity, blood pressure, inflammation, and insulin resistance in African-American adolescents.

Samuel S Gidding

Robert A. Palermo DO
LVHN, Robert_A.Palermo@lvhn.org

Stephanie S DeLoach

Scott W Keith

Bonita Falkner

Published In/Presented At

Gidding SS, Palermo RA, DeLoach SS, Keith SW, Falkner B. Associations of cardiac structure with obesity, blood pressure, inflammation, and insulin resistance in African-American adolescents. Pediatr Cardiol. 2014 Feb;35(2):307-14. doi: 10.1007/s00246-013-0777-2. Epub 2013 Oct 6. PMID: 24096716; PMCID: PMC3946929.

Pediatr Cardiol (2014) 35:307–314
DOI 10.1007/s00246-013-0777-2

ORIGINAL ARTICLE

Associations of Cardiac Structure with Obesity, Blood Pressure, Inflammation, and Insulin Resistance in African-American Adolescents

Samuel S. Gidding · Robert A. Palermo · Stephanie S. DeLoach · Scott W. Keith · Bonita Falkner

Received: 20 May 2013 / Accepted: 13 August 2013 / Published online: 6 October 2013

Abstract To determine if obesity, blood pressure (BP), markers of inflammation, and insulin resistance are associated with cardiac structure in African-American adolescents, a cross–sectional study was performed on a cohort oversampled for high BP and obesity. Measurements included the following: anthropometrics, BP, homeostasis model assessment (HOMA) to assess insulin resistance, high-sensitivity C-reactive protein, and plasma adipokines (adiponectin, interleukin-6, plasminogen activator inhibitor-1). Echocardiogram measurements were left-ventricular mass index (LVMI) ($g/m^{2.7}$), LV relative wall thickness (LVRWT), left-atrial diameter index [LADI (mm/m)], and LV diastolic time intervals. LADI ($r^2 = 0.25$) was associated with body mass index (BMI) systolic BP (SBP) and female sex. LVMI ($r^2 = 0.35$) variation was associated with BMI SBP, heart rate, age, and male sex. LVRWT ($r^2 = 0.05$) was associated with HOMA. Tissue diastolic intervals were not associated with any risk factor. Inflammatory markers and adipokines were associated with BMI but were not independently associated with any echocardiographic measures. In African-American adolescents, BMI and SBP, but not inflammatory markers or adipokines, are important correlates of LA size and LVM.

Keywords Obesity · Inflammation · Adolescents · Left atrium · Left-ventricular mass

Abbreviations

LVM (I)	Left-ventricular mass (index)
LA (DI)	Left atrium (diameter index)
BP	Blood pressure
BMI	Body mass index
TNF-α (R)	Tumor necrosis factor alpha (receptor)
IL-6	interleukin-6
PAI-1	Plasminogen activator
CRP	High sensitivity C-reactive protein
LVDTI	LV diastolic time intervals
HR	Heart rate
HOMA	Homeostasis model assessment
ABPM	Ambulatroy blood pressure monitoring
RWT	Relative wall thickness

Introduction

There are racial differences in the development of cardiovascular disease, with African-Americans being adversely affected. Compared with whites, African-Americans and males have been shown to have increased left-ventricular mass (LVM) [10, 19, 33]. There are inconsistent data regarding the association of insulin resistance with LV and left-atrial (LA) size [22, 26, 34]. Bibbins-Domingo et al. [4] followed-up healthy, young adults >20 years of age and found significantly more cases of heart failure in African-

S. S. Gidding (✉) · R. A. Palermo
Nemours Cardiac Center, Alfred I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: samuel.gidding@nemours.org

S. S. DeLoach
Department of Internal Medicine, Thomas Jefferson University, Philadelphia 19107, PA, USA

S. W. Keith
Division of Biostatistics, Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia 19107, PA, USA

B. Falkner
Division of Nephrology, Thomas Jefferson University, Philadelphia 19107, PA, USA

American young adults than in whites. Obesity and obesity-related risk factors, including high blood pressure (BP), lead to cardiovascular morbidity by way of inflammation and endothelial damage [2]. In African-American adults, DeLoach et al. showed an association between body mass index (BMI) and increased pro-inflammatory adipokine levels [tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), plasminogen activator (PAI-1), and high sensitivity c-reactive protein (CRP)] that was unrelated to BP [11].

We recruited an African-American adolescent cohort oversampled for the presence of obesity and pre-stage 1 and stage 1 hypertension to further assess early cardiovascular and metabolic comorbidities of evolving cardiovascular risk. We previously showed in this cohort that both adverse cardiac structure and markers of inflammation and insulin resistance are strongly associated with intermediate as well as high-risk BP and obesity phenotypes [18]. The purpose of this study was to examine in greater depth these factors and how they are associated with cardiac structure. Associations of cardiac structure with BP, BMI, proinflammatory adipokine profile (low adiponectin, increased IL6, PAI-1, and CRP), insulin resistance, and urinary sodium were investigated.

Methods

Participants

Healthy adolescents, ages 13–18 years (47 % female), were recruited through community advertisements and referral from primary care offices between 2009 and 2011 as part of a study investigating comorbidities of obesity and increased BP in African-Americans. Participants were oversampled for obesity (BMI ≥95th percentile Centers for Disease Control United States graphs) and high risk BP defined as average BP ≥120/80, mmHg [28]. Participants were Tanner stage 4 or greater. Exclusions included secondary hypertension, diabetes, renal disease, cardiovascular disease, autoimmune disease, thyroid disease, sickle cell disease, eating disorders, and use of steroids. Children with stage 2 hypertension or with a history of taking antihypertensive medication were not enrolled. Children taking behavioral medications on a stable regimen (the same dose at each study visit; $n = 5$) were included. The most common medications taken by participants were for asthma, allergies, or birth control. The study protocol was approved by the Institutional Review Boards of Thomas Jefferson University and A. I. DuPont Hospital for Children. Written informed consent was obtained from 18-year-old participants, whereas consent was obtained from the parent or guardian at enrollment and assent obtained from the child if age <18 years.

Study Procedures

Information regarding health status, medication use, and health-related behaviors were obtained by self-report from each participant or guardian. Birth weight was also obtained by self-report. BMI was calculated as weight (kg) divided by height squared (m^2). Obesity was defined as BMI ≥95th percentile for age and sex. BP measurements were obtained by auscultation, with the subject seated, after a 10-min rest and were performed on the right arm using a cuff large enough to encircle 80 % of the subject's upper arm. The average of three successive measurements of systolic BP (SBP) and diastolic BP on two separate visits was used as the BP value. For adolescents with high BP, a third set of BP measurements was obtained to ensure that the average of all BP measurements were ≥120 systolic or ≥80 diastolic mmHg. BP percentiles were also calculated based on population-standardized BP z scores [28]. In a subgroup of adolescents, 24-h ambulatory BP monitoring (ABPM) was performed using the SpaceLabs 90207 device, an oscillometric BP monitor that has been validated in the pediatric population. All participants were Tanner stage 4 or fully mature.

Each participant underwent two-dimensional guided echocardiography to evaluate LA diameter, LV geometry, and LVM. Measurements of the LA diameter, LV internal dimension, interventricular septal thickness, and posterior wall thickness during diastole were made according to methods established by the American Society of Echocardiography [24]. LA diameter was indexed by height (m). LVM was calculated from the equation LVM (g) = 0.81 [1.04 (interventricular septal thickness + posterior wall thickness + LV end-diastolic internal dimension)^3 − (LV end-diastolic internal dimension)^3 + 0.06]. LVM index (LVMI) was calculated as LVM/m^2.[28]. LV hypertrophy in children and adolescents was defined as LVMI ≥95th percentile based on sex-specific normative LVMI data [23]. LV relative wall thickness (RWT) was calculated as the ratio of twice the LV posterior wall thickness in diastole to LV internal diameter in diastole. LV geometry was assessed as normal, concentric remodeling, eccentric LV hypertrophy, or LV hypertrophy with concentric remodeling based on the presence of LVMI above or below the 95th percentile and LVRWT above or below 0.41 [9]. Tissue Doppler analysis of the lateral mitral valve annulus was performed, and values from sequential beats were averaged. Diastolic function was calculated as follows: LV diastolic time intervals (LVDTI) = E/Ea. Heart rate (HR) was calculated from the M-mode tracing. A single echocardiographer and observer (S. G.) performed and interpreted the data related to echocardiographic assessment. Coefficient of variation for intrareader repeat studies ($n = 30$) was 8 % for all variables.

Participants returned to the clinical research unit after an overnight fast. Each participant saved the first morning's voided urine sample (with the time interval from the previous void) and brought the sample to the visit. An indwelling venous catheter was placed, and a fasting blood sample was obtained for laboratory studies. Plasma glucose concentration was analyzed using the glucose oxidase technique (YS model 27; Glucostat, Yellow Springs, OH, USA). Plasma insulin concentration was determined using a solid-phase radioimmunoassay (Coat-a-Count; Diagnostic Products, Los Angeles, CA, USA). Insulin resistance was estimated using the homeostasis model assessment (HOMA) of insulin resistance [27]. Plasma was saved from the fasting blood samples and stored at −80 °C for later assay of adiponectin and the inflammatory cytokines high-sensitivity CRP, IL6, PAI-1, TNF-α, and tumor necrosis factor-alpha receptor [TNF-α (R)]. All assays for the cytokines were performed by enzyme-linked immunosorbent assay in duplicate using commercially available kits. Kits for Adiponectin (total), IL-6, TNF-α, TNF-αR, and CRP were obtained from R&D Systems (Minneapolis, MN, USA). The kits for PAI-1 were obtained from Aniara (Mason, OH, USA). The coefficient of variation for these assays was consistently <10 %, and most were <6 %.

Statistical Analyses

Categorical variables were summarized by frequency counts and percentages. Continuously measured study variables were summarized by measures of central tendency and variability (arithmetic mean and SD if approximately normally distributed or geometric mean and first and third quartiles [Q1, Q3] if substantially skewed). Substantially skewed data were natural log-transformed for all analyses. Univariate comparisons were made for study variables across groups defined by left-atrial diameter index (LADI) tertiles and the four LVMI/LVRWT study groups as defined previously. Analysis of variance (ANOVA) F tests were used to evaluate differences in means, and Fisher's exact tests were used to evaluate differences in proportions. Adjustments were made to these p-values to help control the overall false-positive discovery rate [3]. The significance level for all tests was set in advance at $\alpha = 0.05$.

Multiple regression methods were used to fit models to each of the dependent variables: LADI, LVMI, LVRWT, and LVDTI. For each, we applied a multistage model selection procedure. In the first stage, we regressed the dependent variable on age, sex, BMI z score, SBP z score, and HR in beats per minute (bpm). The residuals from this model were then regressed in the second stage of selection, where we used the hybrid least angle regression method with Mallow's Cp criterion suggested by Efron et al. [17], to select variables that substantially contributed to predicting the dependent variable independently of the contributions from the first-stage model variables. The variables considered in the second stage included HOMA, IL-6, PAI-1, adiponectin, TNF-α, TNF-αR, and CRP. The third stage entailed including the selected variables from second stage into one model with variables from stage 1. Each of the continuous variables was mean-centered before modeling. Results on regression coefficients and 95 % confidence intervals from the full models, including all variables considered, and the selected models are presented. All statistical analyses were performed using SAS version 9.2 (SAS, Cary, NC, USA).

Results

Total enrollment for the study was 301 adolescents; complete data were available for 280 participants in this analysis. Those with incomplete data were phenotypically similar to the analyzed cohort. Forty-eight percent of the participants were female; the mean age was 16 years (range 13–18); the lean normotensive group comprised 37 %, the lean high risk BP group comprised 12 %, the obese normal BP group comprised 34 %, and the obese high-risk BP group comprised 17 % of the cohort. Participant ages ranged from 13 to 18 years of age (mean 16). Sex distribution was similar regarding obesity; however, there were significantly fewer females with high BP (38 %, $p = 0.02$). Age was significantly associated with BP ($p = 0.01$). Data on echocardiographic measures are listed in Table 1. These values are generally comparable with distributions presented in the literature.

Participants were stratified into three groups (low, moderate, high) by tertiles of LADI. Study variables within each LADI group are listed in Table 2. In the univariate analysis, there was a statistically significant association of LADI with BMI ($p < 0.01$), BMI z score ($p < 0.01$), waist circumference ($p < 0.01$), fasting insulin ($p < 0.01$), HOMA ($p < 0.01$), PAI-1 ($p < 0.01$), CRP ($p < 0.01$), and LVMI ($p < 0.01$).

Participants were also stratified according to LV geometry classification. Study variables for each LV geometry group are listed in Table 3. BMI and SBP were significantly associated with LVMI and geometry classification. Relationships of PAI1 and HOMA with increased LVMI were seen; however, the strength of these was weaker than for LADI. Other relationships of marginal significance were seen, but these showed inconsistent patterns. In those with concentric geometry, LVDTI was higher suggesting these individuals may have early diastolic dysfunction.

Further analysis was performed by dividing participants based on BP and BMI designation. Obesity was significantly associated with increased fasting insulin ($p < 0.01$), HOMA ($p < 0.01$), IL6 ($p = 0.01$), PAI-1 ($p < 0.01$), TNF-αR ($p < 0.01$), and CRP ($p < 0.01$) and decreased

Table 1 Echocardiogram data summary by sex

Variable	Mean (SD) or geometric mean [Q1, Q3]		
	All subjects ($N = 280$)	Male ($N = 148$)	Female ($N = 132$)
Aortic root (cm)	2.59 (0.31)	2.67 (0.31)	2.51 (0.30)
Left atrium (cm)	3.34 (0.51)	3.36 (0.49)	3.33 (0.53)
LV dimension/diastole (cm)	4.86 (0.49)	5.03 (0.42)	4.66 (0.49)
LV posterior wall thickness/diastole (cm)	0.87 (0.16)	0.90 (0.15)	0.83 (0.16)
Intraventricular septal thickness/diastole (cm)	0.83 (0.13)	0.88 (0.13)	0.78 (0.12)
LV shortening fraction (%)	36.32 (5.28)	35.53 (5.41)	37.21 (4.99)
LVM (g)	143.07 (41.85)	160.60 (40.94)	123.40 (33.35)
MV E (m/s)	0.97 (0.56)	0.99 (0.75)	0.94 (0.18)
E' (m/s)[a]	0.18 [0.15, 0.20]	0.18 [0.15, 0.20]	0.17 [0.15, 0.20]
DTI ratio	5.66 (1.48)	5.55 (1.41)	5.79 (1.55)

[a] Data were natural log-transformed: geometric means with [Q1, Q3] are presented

Table 2 Summary by tertile-based categories (low, moderate, high) of LADI

Variable	Categorical variables: frequencies (%)			
	Continuous variables: mean (SD) or geometric mean [Q1, Q3]			
	Low (LADI 1.87) ($N = 94$)	Moderate (LADI 1.87–2.12) ($N = 93$)	High (LADI >2.12) ($N = 93$)	Three-way p[a]
Age (year)	16.18 (1.64)	16.14 (1.69)	16.30 (1.72)	0.82
Female sex (%)	39 (41.5)	41 (44.1)	52 (55.9)	0.19
BP ≥120/80 mmHg (%)	26 (27.7)	25 (26.9)	29 (31.2)	0.82
HR (bpm)[b]	70.8 [64, 78]	69.7 [64, 76]	71.8 [64, 80]	0.02
Height (m)	1.71 (0.08)	1.68 (0.09)	1.67 (0.10)	0.01
BMI (kg/m^2)[b]	24.32 [20.44, 27.33]	28.04 [24.89, 32.39]	33.32 [28.58, 39.46]	<0.01
BMI z score	0.78 (1.01)	1.45 (0.91)	1.94 (0.88)	<0.01
Waist circumference (cm)[b]	78.16 [70.00, 87.00]	85.71 [75.00, 97.40]	96.99 [85.00, 114.0]	<0.01
SBP (mmHg)[b]	112.05 [104.3, 121.0]	112.56 [104.7, 120.0]	115.04 [108.7, 122.7]	0.19
SBP z score	−0.23 (0.96)	−0.08 (0.97)	0.20 (0.92)	0.02
DBP (mmHg)[b]	63.52 [59.00, 69.67]	61.50 [56.83, 67.00]	62.21 [57.67, 67.00]	0.25
DBP z score	−0.27 (0.60)	−0.37 (0.70)	−0.33 (0.66)	0.58
HR (bpm)[b]	70.82 [64.0, 78.0]	69.75 [64.0, 76.0]	71.85 [64.0, 80.0]	0.44
HOMA (mg/dl)[b]	1.55 [0.98, 2.21]	1.79 [1.05, 3.38]	2.32 [1.33, 3.52]	0.02
Adiponectin (μg/ml)[b]	6.24 [4.30, 9.30]	5.27 [3.90, 8.20]	5.15 [3.45, 8.65]	0.10
IL6 (pg/ml)[b]	2.78 [1.90, 3.90]	3.06 [2.10, 4.20]	2.95 [2.10, 4.10]	0.61
PAI1 (ng/ml)	50.43 (24.87)	58.86 (27.55)	69.21 (25.63)	<0.01
TNF-α (pg/ml)[b]	8.88 [7.30, 10.60]	8.01 [7.10, 8.90]	8.22 [6.75, 9.55]	0.25
TNF-αR (pg/ml)[b]	0.88 [0.70, 1.10]	0.93 [0.80, 1.20]	0.96 [0.80, 1.20]	0.35
High-sensitivity CRP (mg/dl)[b]	0.51 [0.20, 1.10]	0.77 [0.30, 1.70]	1.13 [0.40, 3.50]	<0.01
LVMI (g/height in m$^{2.7}$)	30.59 (7.06)	34.95 (7.13)	38.27 (7.96)	<0.01
LV RWT (cm/m of height)[b]	0.36 [0.32, 0.41]	0.35 [0.31, 0.41]	0.35 [0.30, 0.39]	0.43
DTI ratio	5.39 (1.23)	5.71 (1.49)	5.89 (1.66)	0.10

[a] Fisher's exact test (categorical) or ANOVA F test (continuous): any groups different (three-way comparison test)

[b] Data were natural log-transformed: geometric means [Q1, Q3] are presented

adiponectin ($p < 0.01$). In contrast, high BP was only significantly associated with increased HOMA ($p = 0.01$) and PAI-1 ($p = 0.02$).

Among the obese adolescents with normal BP, 24 % met echocardiographic criteria for LV hypertrophy based on LVMI >95th percentile [23]. To exclude the possibility

Table 3 Data summary by LV geometry and LVMI groupings

Variable	Categorical variables: frequencies (%)				
	Continuous variables: mean (SD) or geometric mean [Q1, Q3]				
	Normal ($N = 161$)	Concentric remodeling ($N = 32$)	Eccentric LVH ($N = 58$)	Concentric LVH ($N = 29$)	p[a]
Age (year)	16.01 (1.69)	16.40 (1.79)	16.40 (1.70)	16.71 (1.34)	0.13
Female sex (%)	78 (48.4)	18 (56.3)	24 (41.4)	12 (41.4)	0.58
BP ≥120/80 mmHg (%)	31 (19.3)	8 (25.0)	26 (44.8)	15 (51.7)	<0.01
HR (bpm)	71.3 [64, 80]	73.3 [66, 78]	68.6 [62, 78]	69.0 [62, 72]	0.02
Height (m)	1.68 (0.09)	1.67 (0.09)	1.69 (0.09)	1.72 (0.10)	0.25
BMI (kg/m^2)[b]	26.49 [21.97, 31.86]	25.99 [20.69, 32.01]	34.26 [28.26, 42.59]	30.71 [23.79, 37.51]	<0.01
BMI z score	1.19 (1.03)	1.01 (1.16)	2.04 (0.77)	1.62 (0.94)	<0.01
Waist circumference (cm)[b]	82.00 [71.00, 91.75]	82.77 [70.05, 95.24]	99.94 [84.50,118.10]	92.30 [75.50,110.50]	<0.01
SBP (mmHg)[b]	110.98 [105.0,118.00]	113.09 [104.0,120.44]	116.87 [108.3,126.00]	118.77 [109.7,127.33]	0.01
SBP z score	–0.22 (0.84)	0.02 (1.06)	0.26 (1.04)	0.32 (1.11)	0.01
DBP (mmHg)[b]	61.78 [57.67, 67.00]	62.86 [58.67, 67.00]	62.80 [57.67, 69.00]	64.71 [60.00, 69.67]	0.33
DBP z score	–0.35 (0.64)	–0.27 (0.60)	–0.33 (0.76)	–0.21 (0.61)	0.71
HOMA (mg/dl)[b]	1.67 [0.99, 2.71]	1.97 [1.29, 3.40]	2.30 [1.38, 3.92]	2.11 [1.23, 3.26]	0.04
Adiponectin (ug/ml)[b]	5.77 [4.00, 8.70]	5.87 [3.65, 9.69]	5.37 [3.80, 7.50]	4.37 [2.65, 7.50]	0.35
IL-6 (pg/ml)[b]	2.94 [2.00, 4.10]	2.54 [2.00, 3.40]	3.21 [2.20, 4.90]	2.79 [1.95, 3.90]	0.44
PAI1 (ng/ml)	56.60 (25.04)	53.19 (29.45)	69.81 (27.05)	62.13 (30.75)	0.03
TNF-α (pg/ml)[b]	8.48 [7.00, 9.90]	8.28 [7.30, 10.10]	8.51 [6.85, 9.90]	7.57 [6.75, 8.90]	0.46
TNF-αR (pg/ml)[b]	0.92 [0.70, 1.10]	0.91 [0.60, 1.10]	0.97 [0.80, 1.20]	0.86 [0.70, 1.05]	0.48
High-sensitivity CRP (mg/dl)[b]	0.66 [0.20, 1.70]	0.87 [0.30, 1.95]	1.18 [0.60, 3.15]	0.65 [0.24, 1.77]	0.04
LVMI (g/height in m$^{2.7}$)[b]	30.24 (5.24)	31.04 (5.15)	43.10 (3.63)	45.61 (5.26)	
LV RWT (cm/m of height)[b]	0.32 [0.29, 0.36]	0.46 [0.42, 0.48]	0.34 [0.32, 0.38]	0.47 [0.42, 0.49]	
DTI ratio	5.38 (1.35)	6.39 (1.76)	5.69 (1.50)	6.43 (1.33)	0.01

[a] High LVMI = ≥36.9 (females), 39.4 (males); high LVRWT = ≥0.41

[b] Fisher's exact test (categorical) or ANOVA F test (continuous): any groups different (four-way comparison test)

[c] Data were natural log-transformed: geometric means with [Q1, Q3] are presented

of masked hypertension accounting for LV hypertrophy in this group, a sample of the obese normal BP adolescents with and without LV hypertrophy were recalled for 24-h ambulatory BP monitoring. Ambulatory BP monitoring studies were completed on 51 obese normotensive adolescents, including 23 with and 28 without LV hypertrophy. There were no differences in BMI or average BP between those with and without LV hypertrophy. There were also no differences in any of the ambulatory BP monitoring parameters, and no cases of masked hypertension were detected.

Table 4 lists the results of linear regression models to identify correlates of LADI, LVMI, and LVRWT. After model selection, variation in LADI was significantly associated with BMI ($\beta = 0.13$, $p < 0.01$), female sex ($\beta = 0.08$, $p = 0.02$), and SBP z score ($\beta = 0.05$, $p = 0.02$); LVMI variation was significantly associated with BMI z score ($\beta = 3.63$, $p < 0.01$), age ($\beta = 0.70$, $p < 0.01$), female sex ($\beta = -3.65$, $p < 0.01$), SBP ($\beta = 1.09$, $p = 0.02$), and inversely with HR ($\beta = -0.13$, $p < 0.01$) . Although significant in the univariate models, inflammatory markers were not significantly associated with LADI or LVMI after adjustment for other variables, particularly BMI. LVRWT was weakly associated with HOMA ($\beta = 0.02$, $p = 0.01$). For LV DTI, only a weak correlation with TNF-αR was present.

Discussion

The major finding of this study is that BMI is the factor most strongly associated with LADI and LV structure in a cohort of African-American adolescents. BMI is associated with a proinflammatory adipokine profile and HOMA. In univariate analyses, inflammatory factors and HOMA were associated with LADI and LV structure. However, after

Table 4 Full and reduced linear regression models of cardiac measurements

Variable	LVMI				LADI				LVRTW			
	Full ($R^2 = 0.36$)		Reduced ($R^2 = 0.35$)		Full ($R^2 = 0.26$)		Reduced ($R^2 = 0.25$)		Full ($R^2 = 0.06$)		Reduced ($R^2 = 0.05$)	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Intercept	36.21	<0.01	36.14	<0.01	1.95	<0.01	1.95	<0.01	0.36	<0.01	0.36	<0.01
Age	0.76	<0.01	0.70	<0.01	>−0.01	0.75	>−0.01	0.81	0.005	0.10	<0.01	0.12
Sex	−3.81	<0.01	−3.65	<0.01	0.08	0.03	0.08	0.02	0.002	0.85	<0.01	0.91
BMI *z* score	3.79	<0.01	3.63	<0.01	0.12	<0.01	0.13	<0.01	−0.01	0.71	−0.01	0.36
SBP *z* score	0.97	0.04	1.09	0.02	0.04	0.03	0.05	0.02	0.01	0.11	0.01	0.14
HR	−0.12	<0.01	−0.13	<0.01	>−0.01	0.37	>−0.01	0.47	<0.01	0.80	>−0.01	0.98
log HOMA	0.91	0.17			>−0.01	0.97			0.02	0.01	0.02	0.01
log IL6	0.67	0.37			0.01	0.77			−0.01	0.57		
PAI1	>−0.01	0.86			<0.01	0.28			>−0.01	0.33		
Adiponectin	0.13	0.30			0.01	0.29			>−0.01	0.49		
log TNF-α	−1.69	0.13			−0.03	0.58			0.01	0.69		
log TNF-αR	−1.23	0.31			−0.10	0.05	−0.09	0.07	−0.01	0.40		
log high-sensitivity CRP	−0.32	0.43			0.01	0.66			>−0.01	0.86		

adjustment for BMI, these associations disappeared. BP was also associated with heart size and geometry but to a lesser extent than BMI. HOMA had a weak relationship to LVRWT. The magnitude of these relationships to BMI and BP are similar to results of other epidemiologic studies in this age group [31, 33]. LV DTI was generally unrelated to cardiovascular risk factors, although a weak relationship to those with concentric geometry was seen. ABPM in a subset of the cohort with increased LV mass excluded masked hypertension as a cause. To our knowledge, this is the first study to evaluate the association of cardiovascular risk factors, inflammatory markers, adipokines, and insulin resistance with echocardiographic measurements in African-American adolescents.

Enlargement of the left atrium in adults predicts increased cardiovascular morbidity (heart failure, stroke, atrial fibrillation) and mortality [30, 36]. LA volume index has been shown to provide similar predictability for heart failure, hospitalization, and mortality as LV ejection fraction in adults with coronary artery disease [30]. In children, BMI *z* score has been reported to be independently associated with LA size [1, 37]. In hypertensive adults, LA size increases as a function of body size [8], In Native American adolescents, similar relationships to LA size have been found [6]. These associations are important because data from the Bogalusa Heart Study have shown that, compared with whites, African-Americans are more likely to become hypertensive with the onset of hypertension occurring at a younger age [32]. Further study is needed on LADI as a marker of cardiac target-organ injury at a young age.

LV hypertrophy is a manifestation of target-organ injury detectable in children with hypertension [28]. LV hypertrophy is associated with increased BMI and BP, and associations similar to those found in this study have been previously published [6, 33]. A recent study has shown that greater birth weight is also associated with increased LVM [21]. In this study, no significant associations of birth weight with LVM were detected (data not shown). However our data on birth weight were obtained by self-report of the parent, guardian, or participant and were not verified in birth records. Moreover, birth weight could not be recalled in 30 % of the participants. Therefore, associations of birth weight with cardiac mass could not be determined in our African-American adolescent cohort. Among African-American adults with LV hypertrophy, there is a significant increase in cardiovascular mortality independent of BMI and BP [25]. The adolescent participants with high BP in this study did not have clinically confirmed hypertension, and most had average BP levels in the range of prehypertension. The results of this study demonstrate that BMI and BP related target organ injury to the heart occurs early in life in association with modest increases in BP.

Correlates of LVRWT have not been studied in younger generally healthy individuals. Most studies that examine these cardiac parameters have been in children with chronic hypertension or severe obesity; these children have significantly increased LVRWT and abnormal cardiac geometry, particularly those with hypertension [7, 13, 29]. Increased BP at night on ambulatory monitoring may contribute to concentric remodeling. A recent population-

based Italian study showed a relationship of increased triglyceride-to-high-density lipoprotein ratio (a marker of insulin resistance) with LVRWT [14]. Body adiposity may also be correlated with LVRWT [20]. In our cohort, in which adolescents with severe obesity and chronic hypertension were excluded, we found a weak relationship of LVRWT with insulin resistance as estimated by HOMA. Collectively, the results of these studies suggest that chronic exposure to severe obesity and/or hypertension may have a significant impact on LVRWT. Among adolescents with less severe BP increase or obesity, insulin resistance may also have a subtle impact.

Pulsed-wave tissue Doppler imaging is used to assess ventricular function by measuring regional systolic and diastolic myocardial velocities [5]. LVDTI assessment of diastolic function is load independent compared with conventional pulsed wave Doppler measurement. In this study, no significant associations with BP, BMI, or other risk markers were identified. LVTDI was increased in those with concentric geometry suggesting that diastolic function may be affected in those with excess LV wall thickness for a given degree of LV mass. These findings are consistent with those of Border et al. [5]. We did not find associations with BP or BMI as did other studies in cohorts with more severe hypertension or obesity [13, 35]. Using different measures of diastolic function than in this study, the Strong Heart Study uncovered associations of adverse diastolic function with obesity and metabolic syndrome in Native American adolescents [6].

Limitations

Because the study is based on a cross-sectional design, only associations can be examined. Children at the extremes of the BP and BMI distributions were excluded. Prospective studies that examine adolescents longitudinally are needed to determine factors that predict increasing LADI and unfavorable LV geometry; inflammatory markers, adipokines, and insulin resistance might emerge as determinants if there is subsequent progression in LADI and LV geometry. More sophisticated echocardiographic function, such as speckle-tracking techniques, might add additional cardiac function information. The sample size of this study is relatively small and limited to one ethnic group; thus, statistical power and generalizability may be limited. Because the cohort was oversampled for obesity and increased BP, we compared the distribution of BMI and BP with the most recent National Health and Nutrition Examination Survey and found that average BMI and BP were higher than those distributions. Thus, the prevalence of adverse LV geometry and distribution of LA size are skewed compared with that of the general African-American adolescent population.

Conclusion

Obesity and obesity development are strongly associated with future hypertension; thus, the inflammatory milieu associated with obesity described in this study could contribute to injury to the microcirculation, a more rapid increase of BP with aging, and further cardiac end-organ injury [12, 15]. Obesity is associated with increased cardiac index and hyperdynamic circulation [16]. Whether these consequences are sufficient by themselves or are mediated by other obesity-associated metabolic changes is difficult to assess from the results of current clinical studies. Regardless, the evolution of adverse cardiac structure begins in youth. Further longitudinal studies will be important to better understand the complex mechanism of adverse changes in LV geometry and LA size in African-Americans and other ethnic groups.

Acknowledgments This study was funded by the National Institutes of Health/ National Heart, Lung and Blood Institute, Grant no. HL092030.

References

1. Ayer JG, Sholler GF, Celermajer DS (2010) Left atrial size increases with body mass index in children. Int J Cardiol 141:61–67
2. Balagopal PB, de Ferranti SD, Cook S, Daniels SR, Gidding SS, Hayman LL et al (2011) Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. Circulation 123:2749–2769
3. Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 57(1):289–300
4. Bibbins-Domingo K, Pletcher MJ, Lin F, Vittinghoff E, Gardin JM et al (2009) Racial differences in incident heart failure among young adults. N Engl J Med 360:1179–1190
5. Border WL, Kimball TR, Witt SA, Glascock BJ, Khoury P, Daniels SR (2007) Diastolic filling abnormalities in children with essential hypertension. J Pediatr 150:503–509
6. Chinali M, de Simone G, Roman MJ, Best LG, Lee ET, Russell M et al (2008) Cardiac markers of pre-clinical disease in adolescents with the metabolic syndrome: The Strong Heart Study. J Am Coll Cardiol 52:932–938
7. Daniels SR, Loggie JM, Khoury P, Kimball TR (1998) Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. Circulation 97:1907–1911
8. Daniels SR, Witt SA, Glascock B, Khoury PR, Kimball TR (2002) Left atrial size in children with hypertension: the influence of obesity, blood pressure, and left ventricular mass. J Pediatr 141:186–190
9. de Simone G, Daniels SR, Kimball TR, Roman MJ, Romano C, Chinali M et al (2005) Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. Hypertension 45:64–68
10. Dekkers C, Treiber FA, Kapuku G, Van Den Oord EJ, Snieder H (2002) Growth of left ventricular mass in African American and European American youth. Hypertension 39:943–951

11. DeLoach S, Huan Y, Keith SW, Martinez Cantarin MP, Falkner B (2011) Relationship of blood pressure and obesity with inflammatory cytokines among African Americans. Ther Adv Cardiovasc Dis 5:149–157
12. DeLoach SS, Daskalakis C, Gidding S, Falkner B (2012) Central blood pressures are associated with left ventricular mass index among African-American adolescents. Am J Hypertens 25:41–45
13. Dhuper S, Abdullah RA, Weichbrod L, Mahdi E, Cohen HW (2011) Association of obesity and hypertension with left ventricular geometry and function in children and adolescents. Obesity (Silver Spring) 19:128–133
14. Di Bonito P, Moio N, Scilla C, Cavuto L, Sibilio G, Sanguigno E et al (2012) Usefulness of the high triglyceride-to-HDL cholesterol ratio to identify cardiometabolic risk factors and preclinical signs of organ damage in outpatient children. Diabetes Care 35:158–162
15. Dorresteijn JA, Visseren FL, Spiering W (2012) Mechanisms linking obesity to hypertension. Obes Rev 13:17–26
16. Dustan HP (1991) Obesity and hypertension. Diabetes Care 14:488–504
17. Efron B, Hastie T, Johnstone I, Tibshirani R (2004) Least angle regression (with discussion). Ann Stat 32:407–499
18. Falkner B, Deloach S, Keith SW, Gidding SS (2013) High risk blood pressure and obesity increase the risk for left ventricular hypertrophy in African-American adolescents. J Pediatr 162:94–100
19. Gardin JM, Wagenknecht LE, Anton-Culver H, Flack J, Gidding S, Kurosaki T et al (1995) Relationship of cardiovascular risk factors to echocardiographic left ventricular mass in healthy young black and white adult men and women. The Cardia study. Coronary Artery Risk Development in Young Adults. Circulation 92:380–387
20. Gutin B, Treiber F, Owens S, Mensah GA (1998) Relations of body composition to left ventricular geometry and function in children. J Pediatr 132:1023–1027
21. Hietalampi H, Pahkala K, Jokinen E, Ronnemaa T, Viikari JS, Niinikoski H et al (2012) Left ventricular mass and geometry in adolescence: early childhood determinants. Hypertension 60:1266–1272
22. Hirschler V, Acebo HL, Fernandez GB, de Lujan Calcagno M, Gonzalez C, Jadzinsky M (2006) Influence of obesity and insulin resistance on left atrial size in children. Pediatr Diabetes 7:39–44
23. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR (2009) Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr 22:709–714
24. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18:1440–1463
25. Liao Y, Cooper RS, McGee DL, Mensah GA, Ghali JK (1995) The relative effects of left ventricular hypertrophy, coronary artery disease, and ventricular dysfunction on survival among black adults. JAMA 273:1592–1597
26. Litwin M, Sladowska J, Syczewska M, Niemirska A, Daszkowska J, Antoniewicz J et al (2008) Different BMI cardiovascular risk thresholds as markers of organ damage and metabolic syndrome in primary hypertension. Pediatr Nephrol 23:787–796
27. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
28. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114:555–576
29. Richey PA, Disessa TG, Somes GW, Alpert BS, Jones DP (2010) Left ventricular geometry in children and adolescents with primary hypertension. Am J Hypertens 23:24–29
30. Ristow B, Ali S, Whooley MA, Schiller NB (2008) Usefulness of left atrial volume index to predict heart failure hospitalization and mortality in ambulatory patients with coronary heart disease and comparison to left ventricular ejection fraction (from the Heart and Soul Study). Am J Cardiol 102:70–76
31. Schieken RM, Schwartz PF, Goble MM (1998) Tracking of left ventricular mass in children: race and sex comparisons: The MCV Twin Study. Medical College of Virginia. Circulation 97:1901–1906
32. Toprak A, Wang H, Chen W, Paul T, Ruan L, Srinivasan S et al (2009) Prehypertension and black-white contrasts in cardiovascular risk in young adults: Bogalusa Heart Study. J Hypertens 27:243–250
33. Urbina EM, Gidding SS, Bao W, Pickoff AS, Berdusis K, Berenson GS (1995) Effect of body size, ponderosity, and blood pressure on left ventricular growth in children and young adults in the Bogalusa Heart Study. Circulation 91:2400–2406
34. Urbina EM, Gidding SS, Bao W, Elkasabany A, Berenson GS (1999) Association of fasting blood sugar level, insulin level, and obesity with left ventricular mass in healthy children and adolescents: The Bogalusa Heart Study. Am Heart J 138:122–127
35. Van Putte-Katier N, Rooman RP, Haas L, Verhulst SL, Desager KN, Ramet J et al (2008) Early cardiac abnormalities in obese children: importance of obesity per se versus associated cardiovascular risk factors. Pediatr Res 64:205–209
36. Vaziri SM, Larson MG, Benjamin EJ, Levy D (1994) Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation 89:724–730
37. Yu JJ, Yeom HH, Chung S, Park Y, Lee DH (2006) Left atrial diameters in overweight children with normal blood pressure. J Pediatr 148:321–325