Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 378–382

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Racial differences in myocardial deformation in obese children: Significance of inflammatory state

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Received 13 November 2018; received in revised form 21 January 2019; accepted 24 January 2019
Handling Editor: Jonathan Bella
Available online 2 February 2019

KEYWORDS
Obesity;
Pediatrics;
Longitudinal strain;
Metabolic syndrome;
Race

Abstract *Background and aims:* The association between racial differences in myocardial deformation and cardiometabolic risk factors is unknown in obese children. Our objective was to: 1) investigate for racial differences in myocardial deformation between white and black obese children and 2) identify biomarkers associated with these observed racial differences. We hypothesized that decreased myocardial deformation observed in black obese children could be accounted for by the differences in the markers of metabolic syndrome between the groups.
Methods and results: Obese children were recruited prospectively. All clinical and laboratory tests for the metabolic syndrome were conducted during a single assessment using a standardized protocol. Speckle-tracking echocardiography was performed to obtain longitudinal and circumferential measures of deformation. 310 patients were included in the analysis; 158 (51%) white and 152 (49%) black. The median age was 11.3 years (IQR 5.9). Blacks demonstrated worse longitudinal strain ($-14.7 \pm 2.7\%$ vs. $-15.4 \pm 2.9\%$, $p = 0.04$). There was no difference in circumferential strain between the groups. Multivariable linear regression showed a significant relationship between longitudinal strain and hsCRP ($\beta = 0.16$, $p = 0.03$) and HOMA-IR ($\beta = 0.15$, $p = 0.04$); there was no independent association between longitudinal strain and race.
Conclusion: Black subjects demonstrated worse longitudinal strain than whites. Only hsCRP and HOMA-IR levels, not race, had an independent association with longitudinal strain, suggesting that the observed racial differences in longitudinal strain may be secondary to differences in inflammation and insulin resistance between the groups.

Introduction

Cardiovascular disease outcomes are worse for black adults than white for adults [1–4]. Obesity is one of the known major risk factors for cardiovascular disease [5] and is similarly more prevalent in black adults than in white adults [6]. There is increasing evidence that childhood obesity is a risk factor for cardiovascular disease as an adult. However, specific modifiable risk factors in childhood that contribute to the racial differences seen in adults cardiovascular disease are not entirely clear [7].

Racial differences in cardiovascular risk have been observed in the pediatric population. Black adolescents are more likely to be obese, hypertensive, and have higher carotid intima-media thickness (cIMT) and aortic stiffness than whites [8–11]. However, the effect of obesity and the

Abbreviations: BMI, body mass index; cIMT, carotid intima-media thickness; CS, circumferential strain; DXA, dual-energy x-ray absorptiometry; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high sensitivity c-reactive protein; LS, longitudinal strain.

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https://doi.org/10.1016/j.numecd.2019.01.013

consequences of the metabolic syndrome on cardiac function have been incompletely described in children. Moreover, evaluations for racial differences in cardiac function and the metabolic drivers that contribute to these differences have not been studied. The use of speckle-tracking echocardiography to evaluate pre-clinical evidence of cardiovascular dysfunction allows such investigations to now be performed in children.

Our objectives were to: 1) investigate for racial differences in myocardial deformation between white and black obese children and 2) identify biomarkers of the metabolic syndrome that are associated with these observed racial differences. We hypothesized that black children would have poorer myocardial deformation compared to whites and that markers of the metabolic syndrome would be associated with the racial differences observed.

Methods

This was a secondary analysis of a prospective single-institution cross-sectional study whose aim was to assess for racial differences in biomarkers of the metabolic syndrome [10,12,13]. Demographic, echocardiographic, and laboratory data was obtained at our institution from September 2009 through June 2015. This study was approved by the institutional review board of the Medical University of South Carolina. At the time of the original study, informed consent was obtained from patients $\geq$18 years old or from parents or legal guardians for patients $<$18 years old with simultaneous assent obtained from the patient if they were $\geq$12 years old.

Patient selection

All participants were recruited through our institution's Heart Health program, a pediatric obesity management program. Subjects consisted of obese (body mass index [BMI] $>$ 95th percentile) children and young adults aged 4–21 years and of non-Hispanic white or black race. Patients who were pregnant, insulin dependent, or taking chronic oral steroids (for a duration $>$ two weeks) were excluded in this analysis.

Study procedures

All tests were conducted during a single outpatient visit using a standardized protocol. Study visits were rescheduled in case of fever within 72 h of planned study date. Fasting status was confirmed prior to phlebotomy. Age, sex, race, height, weight, blood pressure (DINAMAP automatic cuff, GE Healthcare), fasting insulin, glucose, lipid panel, and high sensitivity c-reactive protein (hsCRP), and body composition by dual-energy x-ray absorptiometry (DXA) were obtained. Body mass index was calculated as weight (kg)/height $(m)^2$. Insulin resistance was determined by calculating the homeostatic model assessment of insulin resistance (HOMA-IR): [glucose (mg/dL) x insulin (mIU/mL)]/405.

Echocardiographic analysis

A single cardiac sonographer performed transthoracic echocardiography in accordance with the guidelines and standards for pediatric echocardiograms by the American Society of Echocardiography using a Philips iE33 ultrasound system (Andover, MA [14]). Echocardiograms were retrospectively obtained from the clinical server (Xcelera, Philips Medical Systems, Andover, Mass) and analyzed by a single blinded reviewer. Speckle-tracking echocardiography was performed using Cardiac Performance Analysis v. 3.0 (Tomtec, Munich, Germany) on DICOM images to obtain longitudinal and circumferential measures of deformation. All measurements were done on the left ventricle (LV). Longitudinal measurements were obtained by manually tracing the endocardium from the mitral valve annulus from the lateral side down to the apex and back to the septal side of the annulus in systole in a four chamber apical view. The area of interest was divided by the software into six segments that were then averaged to estimate the longitudinal strain (LS). A sample analysis of LV LS is shown in Fig. 1. Similarly, the circumferential measurements were obtained by manually tracing the endocardium in a parasternal short axis view and then using the software to calculate the circumferential strain (CS). If two or more segments could not be tracked due to poor acoustic windows, the calculations for that patient were excluded from analysis. Only patients with less than two untrackable segments for LS were included in the analysis.

Statistical analysis

The Shapiro–Wilk test was utilized to determine whether data was parametric versus non-parametric. Independent t-tests were used for parametric data, and Mann–Whitney U tests were used for non-parametric data. Statistics are reported using mean and standard deviation for normally distributed data and median and interquartile range for non-normally distributed data. Pearson's or Spearman's correlation were performed as appropriate to determine univariable associations between strain measurements and independent variables which included age, sex, race, blood pressure, BMI Z-score, HOMA-IR, lipid results, and hsCRP. Stepwise multivariable linear regression was then performed to assess the relationship of myocardial measures of deformation to independent variables. Independent variables were initially considered for the regression model if $p < 0.20$ on univariable analysis (or if $p < 0.20$ when comparing strain between two categorical variables, like sex or race) and were included in the final model if $p > 0.10$ and inclusion increased the explanatory power of the model by 0.03. Intra- and inter-observer variability was assessed using intraclass correlation coefficients measuring absolute agreement to the mean. Statistics were performed using SPSS v24 (IBM Corp., Armonk, NY).

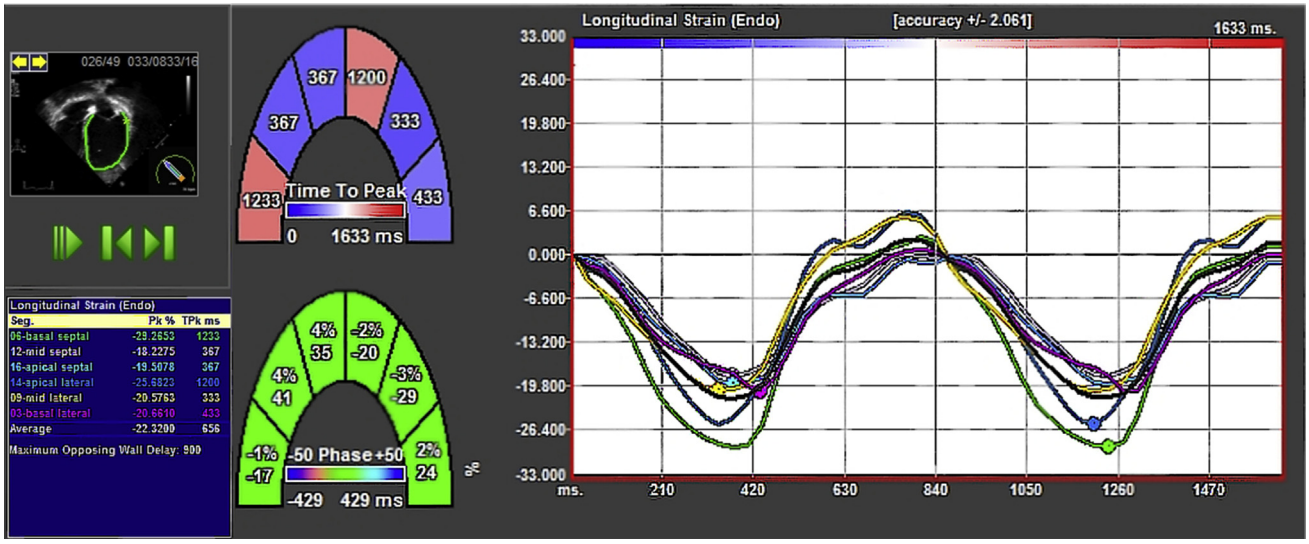

Figure 1 Assessment of longitudinal strain. Speckle-tracking analysis to determine longitudinal strain (bottom strain curves) using Cardiac Performance Analysis v. 3.0 (Tomtec Imaging Systems, Unterschleissheim, Germany).

Results

Of 359 patients eligible for this study, 49 (14%) were excluded due to poor windows precluding speckle-tracking analysis of LS. A total of 310 obese pediatric patients were included in the analysis; 158 (51%) patients were white and 152 (49%) were black. Patient characteristics including demographic, anthropomorphic, laboratory, and echocardiographic data are detailed in Table 1. Black obese children demonstrated worse (less negative) longitudinal strain (−14.7 ± 2.7 vs. −15.4 ± 2.9, p = 0.04). There was no difference in circumferential measures of deformation between races. Males displayed worse strain compared to females (−14.5 ± 2.9% versus −15.4 ± 2.7%, p = 0.004). There was no difference in circumferential measures of deformation between sexes. Intra- and inter-observer variability were r = 0.90 and 0.79, respectively.

Univariable analysis

There was a statistically significant correlation between LV LS and BMI Z-score (r = 0.16, p = 0.008). The associations of LV LS and age (r = 0.08, p = 0.16), systolic blood pressure (r = 0.10, p = 0.16), hsCRP (r = 0.13, p = 0.06), and HOMA-IR (r = 0.12, p = 0.06) all approached statistical significance. Diastolic blood pressure, total cholesterol, triglycerides, HDL, LDL, VLDL, glucose level, total cholesterol:HDL, and triglycerides:HDL had no association with LV LS.

Multivariable analysis

Stepwise multivariable linear regression was performed to assess the relationship of longitudinal strain to age, sex, race, systolic blood pressure, BMI Z-score, HOMA-IR, and hsCRP. The only measures found to have a significant independent association with longitudinal strain were hsCRP (B = 0.94, SE = 0.42, β = 0.16, p = 0.03) and HOMA-IR (B = 0.08, SE = 0.04, β = 0.15, p = 0.04). Race and sex were not independently associated with longitudinal strain after hsCRP and HOMA-IR were accounted for.

Discussion

The main finding of this study is that black obese children had worse myocardial deformation measured by speckle-tracking echocardiography than white obese children. These differences were no longer significant when

Table 1 Patient characteristics.

	White (n = 158)	Black (n = 152)	p-value
Age (years)	11.1 ± 13.7	11.7 ± 8.7	0.42
Female, n (%)	90 (57%)	84 (55%)	0.56
Height (cm)	153 ± 19	153 ± 16	0.89
Weight (kg)	71.5 ± 28.5	84.0 ± 33.0	<0.01
BMI Z-score	1.7 ± 1.1	2.3 ± 0.5	<0.01
SBP (mm Hg)	109 ± 14	112 ± 15	0.17
DBP (mm Hg)	63 ± 9	62 ± 9	0.90
% body fat	38.8 (9.0)	40.9 (7.2)	0.02
Insulin (μIU/mL)	25.0 (19.8)	31.1 (18.0)	<0.01
Glucose (mg/dL)	92 ± 11	93 ± 7	0.30
Cholesterol	166 ± 31	161 ± 27	0.15
HDL (mg/dL)	47 ± 12	45 ± 10	0.13
Triglycerides (mg/dL)	101 (70)	69 (35)	<0.01
LDL (mg/dL)	99 ± 27	102 ± 25	0.21
VLDL (mg/dL)	20 ± 12	14 ± 6	<0.01
Cholesterol/HDL	3.5 (1.3)	3.6 (1.3)	0.50
Triglycerides/HDL	1.8 (1.9)	1.5 (1.0)	<0.01
HOMA-IR	5.9 (4.4)	7.2 (4.8)	<0.01
hsCRP (mg/dL)	0.27 (0.35)	0.50 (0.65)	<0.01
LV LS (%)	−15.4 ± 2.9	−14.7 ± 2.7	0.04
LV CS (%)	−21.9 ± 4.2	−21.8 ± 4.1	0.89

Values reported as mean ± standard deviation or median (interquartile range). BMI = body mass index. CRP = c-reactive protein. CS = circumferential strain. DBP = diastolic blood pressure. HDL = high density lipoprotein. HOMA-IR = Homeostatic model assessment − insulin resistance. LDL = low density lipoprotein. LS = longitudinal strain. LV = left ventricle. SBP = systolic blood pressure. VLDL = very low density lipoprotein.

systemic inflammation and insulin resistance were accounted for. This suggests that the differences in myocardial deformation between white and black children may be driven by the differences in inflammation and insulin resistance between groups.

Speckle-tracking echocardiography has emerged as a tool to help identify early changes in myocardial function. An association between obesity and worse myocardial strain is well documented in children [15–26]. However, to our knowledge, this is the first study to assess for potential racial differences in measures of myocardial deformation in children. Our findings are line with previous studies in adults. Kishi et al. performed a prospective study looking at sex and race differences in 3,499 American black and white adults. At 43–55 years of age, they found worse myocardial deformation in black males using speckle-tracking echocardiography [27]. Based on our findings, it appears these differences start early and can be detected in childhood.

The racial differences in inflammatory markers and insulin resistance between white and black obese patients are well known [28,29]. The causes of these differences are currently being studied, with some groups positing that they may be secondary to differences in adipose tissue distribution (subcutaneous versus visceral) or genetic differences that cause inherent differences in beta cell function between races [30,31]. The effect of these metabolic aberrations on myocardial contractility and stiffness are well studied [32]. Abnormal insulin resistance results in limited adaptive energy response when stress requires a change from free fatty acid metabolism to glucose oxidation. This results in increased oxygen consumption and decreased efficiency [33]. Chronic low-grade inflammation is known to be associated with increased afterload related to micro- and macro-vasculopathies [34]. These studies support the association found in this study between insulin resistance/inflammation and abnormal myocardial deformation.

Clinical implications

An increasing body of evidence has demonstrated that elevated inflammatory markers and insulin resistance in obese individuals put them at an increased risk for cardiac events [35–41]. Elevated CRP values in patients with atherosclerosis is associated with poor cardiovascular outcomes in adults [42]. Multiple studies have detected elevated CRP levels in obese children [27–29,31]. Our study found that these markers of the metabolic syndrome were associated with myocardial deformation. If future studies show that myocardial deformation in childhood is associated with cardiovascular outcomes in adulthood, speckle-tracking echocardiography may have the potential to be used as an imaging biomarker to detect children at risk for heart disease in adulthood.

Limitations

The primary limitation of our study lies in its nature as a retrospective review. While useful for identifying associations between the studied variables, a causative relationship cannot be ascertained. For example, though we found that racial differences in markers of the metabolic syndrome are associated with differences in myocardial deformation between the groups, we cannot determine if these findings are associated with the known differences in cardiovascular disease outcomes between white and black patients in adulthood. We also faced the challenge of the limited acoustic windows in obese children, which made measurements using speckle-tracking echocardiography more difficult and on occasion futile. The univariable and multivariable associations we found were weak. However, that is likely to be expected as the length of time our patients have been obese and the resultant metabolic derangements associated with obesity are low compared to adult studies.

Conclusion

Black obese pediatric subjects demonstrated worse longitudinal strain than whites. They were also found to have higher levels of systemic inflammation and insulin resistance than whites. Only hsCRP and HOMA-IR had an independent association with longitudinal strain; race did not. This suggests that the observed racial differences in longitudinal strain may be secondary to differences in inflammation between the two groups. Further investigations into the etiology of the effects on inflammation and insulin resistance on cardiac function in obese children are warranted. Future studies should assess whether decreased myocardial deformation in obese children is associated with worse cardiovascular outcomes in adulthood.

Potential conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

Funding

This project was supported by the South Carolina Clinical & Translational Research (SCTR) Institute, NIH/NCRR grants UL1 RR029882 and UL1 TR000062.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

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