Markers of Cardiovascular Risk, Insulin Resistance, and Ventricular Dysfunction and Remodeling in Obese Adolescents

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Objectives To test our hypothesis that obese adolescents have left ventricular (LV) dysfunction and remodeling that are associated with markers of cardiovascular risk and insulin resistance (IR).

Study design In a cross-sectional study of 44 obese and 14 lean age-, sex-, Tanner stage-, and race-matched adolescents, IR, markers of cardiovascular risks, conventional and 2-dimensional speckle tracking echocardiography measures of LV function and structure were evaluated and compared.

Results The obese adolescents had significantly increased body mass index Z-score, systolic blood pressure, fasting insulin, IR, and atherogenic lipids compared with the lean adolescents. A subgroup of obese adolescents had LV remodeling characterized by significantly increased LV mass index ($g/m^{2.7}$) and relative wall thickness. Almost all obese adolescents had LV dysfunction with peak LV global longitudinal strain (GLS, %), systolic GLS rate (GLSR, %/s), and early diastolic GLSR significantly lower than in lean adolescents and in the normal pediatric population. Body mass index Z-score predicted LV remodeling (LV mass index [R^2 = 0.34] and relative wall thickness [R^2 0.10]), and peak LV GLS (R^2 0.15), and along with systolic blood pressure, predicted systolic GLSR (R^2 0.16); ($P \leq .01$ for all). Fasting insulin predicted early diastolic GLSR (R^2 0.17, $P \leq .01$).

Conclusions Obese adolescents have subclinical ventricular dysfunction associated with the severity of obesity, increased systolic blood pressure, and IR. Ventricular remodeling is present in a subgroup of obese adolescents in association with the severity of obesity. These findings suggest that obesity may have an early impact on the cardiovascular health of obese adolescents. *(J Pediatr 2015;166:660-5)*.

Emerging evidence suggests that obese adults have increased conventional cardiovascular risk factors, hemodynamic load, and neuro-hormonal activation, but those contributing factors cannot entirely explain the reported changes in ventricular structure and function that lead to heart failure.[1,2] There are intrinsic alterations in the myocardium that are independent of load. Insulin resistance (IR) promotes alterations in myocardial substrate metabolism, evident by increases in myocardial fatty acid uptake, utilization, and oxidation that may play a role in the pathogenesis of decreased myocardial efficiency and cardiac dysfunction in obese individuals.[3] Studies in obese children and adolescents have shown ventricular remodeling and subclinical impairment in diastolic function but have not discerned the association between ventricular dysfunction and markers of cardiovascular risks or IR in this population.[4-6]

We measured clinical and metabolic markers of cardiovascular risk and IR, and assessed the left ventricular (LV) structure and function in lean and obese adolescents. Our hypothesis was that obese adolescents have subclinical LV dysfunction and remodeling associated with markers of modifiable cardiovascular risk and IR.

Methods

Using a cross-sectional study approach, we studied a group of obese adolescents (body mass index [BMI] ≥95th percentile for age and sex)[7] referred to the Washington University Outpatient Pediatric Preventive Cardiology Clinic at St. Louis Children's Hospital from January 2007 to December 2012. Subjects were eligible for inclusion if they were 12-18 years of age, Tanner stage III or higher, and had complete echocardiographic and laboratory evaluations performed during the study period. Subjects were excluded if they had heart disease, diabetes, or other endocrinopathies, pregnancy, or a history of substance and alcohol abuse, smoking, obstructive

BMI	Body mass index
GLS	Global longitudinal strain
GLSR	GLS rate
HOMA-IR	Homeostasis model assessment of IR
IR	Insulin resistance
LOA	Limit of agreement
LV	Left ventricular
LVMI	LV mass index
RWT	Relative wall thickness

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Supported in part by the National Institutes of Health (R21 HL106417, 5 T32 HD043010-09, UL1 TR000448). The National Institutes of Health was not involved in the study design, data collection, statistical analysis, writing of the manuscript, or decision to submit this paper for publication. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.11.012

sleep apnea, use of pharmaceutical agents that affect IR, or had a poor acoustic windows for echocardiographic evaluation. A cohort of healthy, lean (BMI <85th and >5th percentile for age and sex), age-, sex-, race-, and Tanner stage-matched (for minimizing the potential confounding effects on IR)[8] subjects from a simultaneous study in our institution was used as a control group.[9] In addition, data from normal healthy, lean, age- (12-18 years) and sex-matched pediatric cohort (n = 51) from our echocardiography laboratory were included to provide the range of normal pediatric values of echocardiographic functional.[10,11] The Institutional Review Board for human studies at Washington University approved the study. Written informed consent was obtained from the parents/guardians of the study subjects.

All subjects underwent a comprehensive clinical evaluation as part of the standard of care. Demographic and anthropometric variables were collected. BMI (kg/m^2) was transformed into BMI Z-score to adjust for age and sex. Three measurements of systemic blood pressure (mm Hg) were taken using a manual sphygmomanometer with the appropriate cuff size in resting position. Hypertension was defined based on the average systolic or diastolic blood pressure percentiles for age, sex, and height: prehypertension (≥90th but <95th), stage I (≥95th but <99th, plus 5 mm Hg), and stage II (>99th, plus 5 mm Hg).[12] The metabolic assessment was performed after a 12-hour overnight fasting and included plasma glucose (mg/dL), plasma insulin (μU/mL), and lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, mg/dL). Dyslipidemia and hyperglycemia were defined according to the published criteria for the pediatric population.[13,14] Variables used to define metabolic syndrome were considered as markers of cardiovascular risk and included BMI Z-score, systemic blood pressure, fasting glucose, and lipid profiles.[15] For IR indices, we used the reciprocals of homeostasis model assessment of insulin sensitivity = 22.4/glucose (mg/dL) × insulin (μU/mL) and the fasting plasma insulin (mL/μU).

Assessment of Cardiac Structure and Function

LV Structure. A transthoracic complete M-mode, 2-dimensional (2D) and Doppler echocardiographic examination was performed with a commercially available ultrasound imaging system using a phased array transducer of appropriate frequency (Vivid 7 and 9; General Electric Medical Systems, Milwaukee, Wisconsin). Using M-mode imaging of the LV in the parasternal short-axis view, relative wall thickness (RWT) and LV mass index (LVMI) (Devereux formula) were calculated and LVMI was indexed to height$^{2.7}$ (g/m$^{2.7}$).[16,17] The 95th percentiles for LVMI for children older than 9 years of age (>40 g/height$^{2.7}$ in females and >45 g/height$^{2.7}$ in males) and the 95th percentile value for RWT for normal children and adolescents (RWT >0.41) were used as cut-off values to categorize LV structure (geometry).[18,19]

LV Function. LV fractional shortening and biplane LV ejection fraction were measured according to the guideline of the American Society of Echocardiography.[16] Myocardial mechanics were analyzed by the quantification of LV longitudinal strain and strain rate. Strain (%) describes the fractional changes in the dimension of a myocardial fiber/segment. Myocardial strain rate (%/s) is the rate of change in strain and represents fiber contractility.[20] LV global longitudinal strain (GLS, %) and systolic and diastolic GLS rates (GLSRs, %/s) were measured by using validated 2-dimensional speckle tracking echocardiography.[21] A single observer, who was blinded to the subjects' clinical and metabolic values analyzed peak LV GLS, systolic GLSR, and early and late diastolic GLSR values using vendor software (EchoPAC; General Electric Medical Systems). Our echocardiography laboratory has previously demonstrated high reproducibility of strain measurements.[21] We further tested the reproducibility of GLS and GLSR in 7 age- (12-18 years), sex- (4 male), and BMI z score- (1.82-2.32) matched obese adolescents at 2 time points at 6-week interval.

Statistical Analyses

Continuous data were tested for normality with the Shapiro-Wilk W test, and equality of variances was tested with the O'Brien, Brown-Forsythe, Levene, Bartlett, and F Tests. The *t* test and the Wilcoxon rank sums test were used for data with normal and non-normal distribution and/or variances, respectively. Because structure and function in the heart are closely linked,[22] the adolescent cohort was further divided into obese with normal LV structure (normal LVMI and RWT, "normal obese") and obese with abnormal LV structure (abnormal LVMI and RWT, "abnormal obese"). Comparisons were made among the "abnormal" and "normal" obese adolescents and lean control groups by using one-way ANOVA, with 2 planned contrasts for the comparisons of interest: obesity (lean vs all obese adolescents) and abnormal LV structure ("normal obese" vs "abnormal obese" adolescents). Bivariate analyses and backward stepwise multiple linear regression analyses were used to determine which variables best predicted changes in LV structure and function for the entire cohort of lean and obese subjects as well as for the cohort of obese subjects only. To predict LV structure and function, BMI Z-score, systolic blood pressure, and fasting insulin were used as independent variables.[9,23,24] The maximum R^2 from K-fold cross validation was used for the multiple linear regression analyses. A P value of ≤.05 was considered statistically significant. Using data on differences in fasting insulin levels between obese and lean children from a previous study[9] and with alpha set at 0.05, a 2-tailed test determined a sample size of 13 in each group and a power of 80.1%. We enrolled more than 13 obese adolescents in the study group at the outset. Statistical analyses were performed with JMP Statistical Software 10.0.0 (SAS Institute, Inc, Cary, North Carolina), StatXact 10 (Cytel, Inc, Cambridge, Massachusetts), and Power and Precision 4.0 (Biostat, Inc, Englewood, New Jersey).

Results

A total of 44 out of 57 obese adolescents were included in this study. Thirteen subjects were excluded because of incomplete laboratory data and inadequate acoustic windows. Fourteen