www.jpeds.com • THE JOURNAL OF PEDIATRICS

Cardiometabolic Phenotype in Children with Obesity

Procolo Di Bonito, MD[1], Nicola Moio, MD[2], Gerolamo Sibilio, MD[2], Luigi Cavuto, MD[2], Eduardo Sanguigno, MD[3], Claudia Forziato, MD[3], Giovanni de Simone, MD[4], and Brunella Capaldo, MD[5]

Objectives To investigate the anthropometric and metabolic correlates of different patterns of left ventricular (LV) geometry in a cohort of outpatient children with high prevalence of obesity.

Study design Anthropometric measures, lipid profile, blood pressure (BP), fasting plasma glucose (FPG), and echocardiographic variables were evaluated in 281 white children (6-16 years), of whom 105 were obese and 105 were morbidly obese. Patterns of LV geometry were defined as follows: normal geometry, eccentric LV hypertrophy (LVH), concentric LV remodeling, and concentric LVH.

Results One hundred forty-eight children exhibited normal LV geometry, 53 eccentric LVH, 36 concentric LV remodeling, and 44 concentric LVH. The 4 groups differed in body mass index, waist circumference, waist-to-height ratio, triglycerides/high-density lipoprotein cholesterol ratio (Tg/HDL-C), and BP ($P < .05$-.0001). A statistically significant impairment of diastolic function (expressed as greater E/E′, $P < .002$) was observed across patterns of LV geometry. Among anthropometric measures, waist-to-height ratio showed better performance in relation to LVH, with an optimal cut-point of 0.58, compared with body mass index and waist circumference. Children with concentric LVH exhibited the worst metabolic risk profile, with greater prevalence of visceral obesity, high Tg/HDL-C, high BP, and high-normal FPG, than children with normal LV geometry.

Conclusions In children with high levels of obesity, an unfavorable "cardiometabolic phenotype" can be identified, which includes concentric LVH, visceral obesity, high BP, high Tg/HDL-C, and high-normal FPG. *(J Pediatr 2014;165:1184-9)*.

Left ventricular (LV) structural changes are associated with increased cardiovascular (CV) morbidity and mortality in adult populations.[1] High levels of LV mass (LVM) and/or of relative wall thickness (RWT) produce distinct CV phenotypes, which reflect an adaptive response of the heart to metabolic and/or hemodynamic stimuli. Knowledge of these geometric patterns has important prognostic implications because eccentric LV hypertrophy (LVH) is thought to be associated with high risk of heart failure, and concentric remodeling and concentric LVH confer a greater risk of coronary heart disease and stroke.[2] The identification of the CV risk factors underlying a specific phenotype of LV geometry is important particularly for the pediatric population in the light of the recent findings of the third National Health and Nutrition Examination Survey, which showed an increased risk of early mortality in adolescents and young adults with visceral obesity, high blood pressure (BP), and high glycosylated hemoglobin.[3]

Several studies have documented a close relationship between increased LVM and overall obesity[4-6] in children and adolescents; in addition, these studies have underlined the relationship of body mass index (BMI) and BP in promoting LV concentric patterns,[7-10] an association already demonstrated in adults.[11] The association of LV geometric abnormalities with other metabolic risk factors, however, such as dyslipidemia and abnormal glucose regulation, has been poorly explored in children. Because the combination of LVH and/or increased RWT produces different geometric patterns with distinct prognostic significance, it is of great interest to examine how early in life these patterns occur and which of them is associated with a proatherogenic risk profile.

In the last few years, there has been a lively debate over which anthropometric measure best reflects high CV risk in childhood.[12,13] To date, no study has compared the performance of BMI or surrogates of visceral obesity, such as waist circumference (WC) and waist-to-height ratio (WhtR) in relation to LVH in children. Accordingly, this observational study was designed to investigate the frequency of abnormal patterns of LV geometry in a large population of outpatient children with high prevalence of obesity and morbid obesity, to test the performance of different

BMI	Body mass index	LVH	Left ventricular hypertrophy
BP	Blood pressure	LVM	Left ventricular mass
CV	Cardiovascular	LVMi	Left ventricular mass indexed for height
FPG	Fasting plasma glucose		
HDL-C	High-density lipoprotein cholesterol	RWT	Relative wall thickness
		TDI	Tissue Doppler imaging
HOMA-IR	Homeostasis model assessment–estimated insulin resistance	Tg	Triglycerides
		WC	Waist circumference
LV	Left ventricular	WhtR	Waist-to-height ratio
LVDD	Left ventricular diastolic diameter		

From the Departments of [1]Internal Medicine, [2]Cardiology, and [3]Pediatrics, Pozzuoli Hospital; and Departments of [4]Translational Medical Sciences and [5]Clinical Medicine and Surgery, Federico II University, Naples, Italy

The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.08.007

anthropometric indices in relation to LVH, and to evaluate whether the observed LV geometric patterns are associated with distinct metabolic risk profiles or subclinical impairment of cardiac function.

Methods

Two hundred eighty one White children were consecutively observed in the Outpatient Unit of the Pediatric Department of Pozzuoli Hospital in the period 2004-2013. They had been referred to our Unit by their General Practitioners because of allergy problems, suspected gastroesophageal reflux, being overweight, or being obese. All subjects were apparently healthy, and none had a previous diagnosis of diabetes, hypertension, secondary obesity, or had any evidence of renal, urinary, and infectious diseases. None of them was or had been receiving pharmacologic treatment, as elsewhere described.[14]

Anthropometric measurements were obtained with standard methods. Weight was determined to the nearest 0.1 kg on a medical balance. Height was measured with a wall-mounted stadiometer by the same investigator, who was specifically trained in anthropometry. WC was measured with the child in a standing position via the use of a flexible tape taken midway between the tenth rib and the iliac crest. WhtR was calculated as the ratio of waist (cm) and height (cm). Sexual maturity was evaluated by the Tanner stage for pubic hair (I-V). BP was measured according to "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents."[15]

After the patient fasted overnight, blood samples were collected for the determination of glucose, insulin, and lipids, which were centrally measured in the laboratory of Pozzuoli Hospital using a ROCHE analyzer (Modular Analytics Serum Work Area, 68298 Mannheim, Germany). Triglycerides/high-density lipoprotein cholesterol ratio (Tg/HDL-C) was calculated from Tg and HDL-C. Plasma insulin was measured by the immunoenzymatic method. Insulin resistance was calculated by homeostasis model assessment–estimated insulin resistance (HOMA-IR) index via a standard formula: fasting insulin (UI/L) $\times$ fasting plasma glucose (mmol/L) divided by 22.5.

Standard echocardiograms were obtained by a commercially available echocardiographic system with tissue Doppler imaging (TDI) capabilities (Artida/Aplio; Toshiba, Tutsin, California). All measurements were analyzed according to the recommendations of the American Society of Echocardiography. We estimated LVM according to the American Society of Echocardiography recommendations[16] using M-mode whenever possible, or optimally oriented 2-dimensional parasternal long-axis view. LVM was therefore indexed for height$^{2.7}$ (LVMi). RWT was calculated from posterior wall thickness, interventricular septum thickness, and LV diastolic diameter (LVDD) via the following formula: (posterior wall thickness + interventricular septum thickness)/LVDD. We defined LVH by 95th percentile of the normal distribution as proposed by Khoury et al[17] using age- and sex-specific quantiles. High levels of RWT were defined using a cut-point of 0.375.[14,18] LV geometry was defined as follows: normal geometry (normal LVMi and RWT), eccentric LVH (increased LVMi and normal RWT), concentric remodeling (increased RWT with normal LVMi), and concentric LVH (increased RWT and increased LVMi). On the basis of reported allometric relations of stroke volume with body height in children and adults, stroke volume was normalized for height$^{1.45}$.[19]

LV function was analyzed by conventional and TDI echocardiography as previously described.[14,20] Transmitral peak rapid filling velocity and peak atrial filling velocity were obtained as measures of diastolic function. For TDI echocardiography, 3 major velocities were recorded at the lateral corner of mitral annulus: peak positive systolic velocity and 2 peak negative velocities during the early and late phases of diastole; the early peak rapid filling velocity to early annular velocity ratio also was calculated. All echocardiographic readings were made online by the same investigator who was blinded to the metabolic status of the children.

Prepubertal stage was defined by Tanner stage I. Overweight, obesity, and morbid obesity were defined using the new partition-values of International Obesity Task Force that correspond to BMI $\geq$25, BMI $\geq$30, and BMI $\geq$35 kg/m^2 at age 18 years.[21] High BP ($\geq$95th percentile for age, sex, and height) was defined according to "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents."[15] An abnormal lipid profile was defined as Tg/HDL-C $\geq$2.0 as previously described.[14] High glucose level was defined as a fasting plasma glucose (FPG) $\geq$89 mg/dL; this cut-off is associated with several CV risk factors, as previously described.[22] The study was approved by the Local Ethics Committee, and informed consent was obtained from the parents of all participants.

Statistical Analyses

Data are expressed as mean $\pm$ SD, or proportions (%). Given the skewed distribution of HOMA-IR and Tg/HDL-C, the statistical analysis of these variables was applied after log-transformation and back transformation to natural units. Means were compared by ANOVA. The χ^2 or Fisher exact test, as appropriate, was used to compare proportions. To analyze the relationship between LVH and anthropometric measures (BMI, WC, and WhtR), we performed 2 types of statistical analysis. First, the performance of different anthropometric measures in relation to LVH was compared by area under receiver operating characteristic curve (AUC) using LVH as binary variable and BMI, WC, and WhtR as continuous variables. The best cut-off of anthropometric measures more strongly associated with LVH was calculated by the Youden index, which represents a global measure of a test performance. This index was calculated with the following formula: sensitivity + specificity $-$ 1.[23] Subsequently, we tested the independent role of WhtR by performing a logistic regression analysis using LVH as dependent variable and Tanner stage, BP, BMI, and WhtR as covariates. A 2-sided