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Left ventricular diastolic function and cardiometabolic factors in obese normotensive children

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Abstract *Background and aim:* Left ventricular (LV) hypertrophy and diastolic function have been found to be associated with obesity and hypertension in adults. However, there are scarce data about the association of obesity itself to cardiac alteration in children. The aim of this study was to detect early changes in LV structure and function in obese children and whether they are associated with the biomarkers of metabolic risk and endothelial activation.
Methods and results: A total of 130 children aged 7–16 years (88 obese and 42 normal-weight children) were studied. All children had normal resting blood pressure. Two-dimensional ultrasound with M-mode imaging was performed to assess the LV mass index (LVMi), calculated as LV mass/height$^{2.7}$, and the peak diastolic of pulmonary venous flow velocity (PVFD). Tissue Doppler imaging was used to analyze ventricular performance through the ratio of the transmitral peak early filling velocity to the early average diastolic peak myocardial velocity (E/E'). The indicators of metabolic control, inflammation, and endothelial cell activation were evaluated. Compared to the controls, the obese subjects had significantly higher LVMi and E/E' and lower PVFD values, the two latest being found especially in severely obese subjects. In the multivariate analysis, the parameters of diastolic function (E/E' and PVFD) were independently associated with obesity, apolipoprotein A1, soluble vascular cell endothelial molecule-1 (sVCAM-1), and retinol-binding protein 4 (RBP4).
Conclusion: An echocardiographic evaluation of diastolic function is a useful tool to detect early cardiac changes in obese children. Emergent cardiovascular risk markers such as apolipoprotein A1, RBP4, and sVCAM-1 are associated with the parameters of diastolic function.

Abbreviations: Apo-A1, apolipoprotein A1; BMI, body mass index; E/E', ratio of transmitral early filling wave between average of the diastolic annular velocity; HOMA-IR, homeostasis model of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LV, left ventricular; LVMi, left ventricular mass index; MAP, mean arterial pressure; PVFD, peak pulmonary venous flow velocity during diastole; RBP4, retinol-binding protein 4; RWT, relative wall thickness; SDS-BMI, standard deviation score of body mass index; sVCAM-1, soluble vascular cell adhesion molecule-1.

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Introduction

Comorbidities associated with obesity such as diabetes and hypertension predispose patients to significant changes in the cardiovascular system. However, in adult subjects, a link has been shown between obesity itself and subclinical cardiac structural changes leading to an "obese cardiomyopathy" syndrome [1]. Several authors have reported associations of obesity with increased left ventricular (LV) wall stress and compensatory LV hypertrophy [2], LV dilation, and even heart failure [3].

Increased body mass index (BMI) in children is associated with early structural myocardial disturbances in adulthood in the form of LV hypertrophy; thus, childhood obesity is an independent risk factor for heart failure in adults [4]. Therefore, childhood obesity should be considered not only a risk factor for cardiovascular diseases in adulthood but also a cause of subclinical impairment of cardiac function in childhood. LV structural changes have already been shown in obese adolescents with hypertension [5], and clinical or subclinical LV dysfunction can be present at this early age [6]. In this sense, both systolic and diastolic cardiac dysfunction have been correlated with the extent of increase in BMI in adolescents [7,8].

The exact mechanisms linking obesity with subsequent cardiac alteration are not fully understood if we exclude hypertension. Moreover, metabolic abnormalities accompanying obesity independent of hypertension are associated with significant cardiac abnormalities in children [9], suggesting that these alterations might be a response not only to increased hemodynamic load but also to neurohormonal or as yet unknown factors influencing LV structure and function.

Recently, both LV hypertrophy and diastolic dysfunction have been found to be associated with systemic inflammation in obese and hypertensive adults [10,11]. This association might be mediated by clinical risk factors that are themselves related to an inflammatory state. In this sense, studies in children represent a great advantage because children are generally free of comorbidities that might be confounding factors.

In the present study, we hypothesized that the biomarkers of metabolic risk, inflammation, and endothelial dysfunction in obese children predict the occurrence of subtle cardiac alterations as target organ damage in the absence of traditionally defined hypertension. For this purpose, we have determined standard echocardiography and tissue Doppler imaging parameters in both normal-weight and obese children without hypertension and have related them to anthropometry, metabolic risk factors, and parameters of inflammation and endothelial cell damage.

Methods

This was a prospective, controlled, cross-sectional study carried out involving 130 children (69 boys) aged 7–16 years, of whom 88 were obese children (48 boys) referred for diagnosis and treatment and 42 were healthy, non-obese children (21 boys) who were age- and sex-matched as controls recruited by primary care pediatricians in the Children's Health Care program. The children's height, weight, and waist circumference were measured following standardized procedures. Obesity was defined as a BMI greater than the 95th percentile for age and gender based on the World Health Organization (WHO) standards. The values were converted to standard deviation scores of BMI (SDS-BMI). The obese children were divided into two groups: SDS-BMI between 2 and 4 and SDS-BMI >4 (severe obesity). The perimeter of the waist was referenced to the 50th percentile for gender and age [12]. Fat-free mass and adipose body mass were estimated by the use of a Tanita impedance meter (model BC-418MA, Tanita Europe BV, Hoofddorp, the Netherlands).

Resting blood pressure was taken in the physician's office from the right arm with the patient seated using an automated oscillometric device (Dinamap; Critikon Inc., Tampa, Finland) and the mean of three measurements was recorded. Hypertension was assessed according to normative values from the 2004 National High Blood Pressure Education Program [13]. Pulse pressure (systolic blood pressure minus diastolic blood pressure) and mean arterial pressure (MAP, diastolic blood pressure plus pulse pressure/3) were estimated. All subjects participating in the study had arterial blood pressure below the 90th percentile in repeated measurements. The exclusion criteria included congenital heart disease, valvulopathy, and primary myocardiopathy in the children or their first-degree relatives. The local research ethics committee approved this study. Written informed consent was obtained from the parents and from children older than 12 years of age.

Echocardiography measurements

A complete echocardiographic study was performed on each child included in the study using a Phillips echocardiography device, model iE33 (Andover, Massachusetts, USA), and a 4-MHz sectorial transducer. All subjects were examined by the same experienced cardiologist (MT) in the left lateral position in the dark, without noise, between 16.00 and 20.00 h. Standard M-mode recordings of the LV dimensions and function were obtained as recommended by the American and European Societies of Echocardiography [14]. The measurements included interventricular septal and posterior wall thickness and LV diameters at the end of systole and at the end of diastole. LV mass was calculated from the Devereux formula [15] and indexed by height$^{2.7}$ (LV mass index, LVMi). LV relative wall thickness (RWT) was calculated as (interventricular septal thickness + posterior wall thickness)/LV diameter in end diastole and was also normalized for age [16]. The evaluation of LV geometry was carried out using the 95th percentile of RWT and LVMi [17] for age and gender and was classified as normal, eccentric hypertrophy, concentric hypertrophy, or concentric remodeling [18].

For the evaluation of diastolic function, several measures were obtained using conventional Doppler tracings of the mitral and the tricuspid valve from an apical four-