

# Early Cardiac Abnormalities in Obese Children: Importance of Obesity *Per Se Versus* Associated Cardiovascular Risk Factors

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**ABSTRACT:** We investigated whether obese children and adolescents have early echocardiographic signs of subclinical cardiac dysfunction and evaluated the respective influence of obesity *per se versus* parameters of carbohydrate and lipid metabolism that are frequently abnormal in obese subjects. The role of tissue Doppler imaging as a screening tool for these abnormalities was explored. Blood pressure and echocardiographic parameters, including tissue Doppler measurements of the septal mitral annulus were evaluated in 49 obese children and adolescents and 45 age and sex matched controls. The respective influence of obesity *versus* parameters of carbohydrate and lipid metabolism was examined with linear regression analysis. Obese subjects showed significantly larger left ventricular wall dimensions (posterior wall, septum, and left ventricular mass index) and signs of early diastolic filling abnormalities on conventional and tissue Doppler echocardiography compared with nonobese subjects. Multiple regression analysis showed that mainly BMI-SD scores and/or body surface area explained significant proportions of the variance of the early cardiac abnormalities. In conclusion, young, obese children and adolescents have significant changes in left ventricular wall dimensions and early diastolic filling compared with nonobese subjects. Obesity *per se* and not the parameters of carbohydrate and lipid metabolism predicted the early cardiac abnormalities. (*Pediatr Res* 64: 205–209, 2008)

The prevalence of overweight and obesity in children is increasing worldwide at an alarming rate in both developing and developed countries (1). In the United States, approximately 31.2% of children (aged 6–11) are overweight of which 15.8% are obese. For adolescents (aged 12–19), 30.9% are overweight of which 16.1% are obese (2). It is well established that obesity is a strong risk factor for cardiovascular morbidity and mortality. Studies in adults using echocardiography, catheterization, and necropsy examinations have shown relations between morbid obesity, structural alterations of the heart and systolic function, which may lead to a clinical syndrome known as “obese cardiomyopathy” (3). However, the relation between obesity and cardiac structure and function in children is less well documented and conflicting results have been reported (4–7). In addition, obesity is associated with a heterogeneity of metabolic abnormalities

(e.g., dyslipidemia (8), insulin resistance (9), hyperglycaemia) and hypertension (10) that may provide a plausible biologic link between obesity and the increased risk of cardiovascular morbidity and mortality. The clustering of these risk factors for cardiovascular disease is referred to as the “metabolic syndrome.” Although the concept and definition of the metabolic syndrome are controversial at the moment, there is no doubt that a cluster of cardiovascular risk factors is present in obese children and adolescents and that their presence increases with worsening obesity (11–13). Little is however known about the relative influence of obesity *per se versus* associated risk factors for cardiovascular disease (more in specific parameters of carbohydrate and lipid metabolism) on cardiac structure and function.

In the present study, we evaluated whether echocardiographic signs of diastolic and systolic dysfunction are already present in obese children and adolescents. Within the obese subjects, we investigated the relative influence of obesity *versus* associated cardiovascular risk factors on these abnormalities. Additionally, we explored the role of tissue Doppler imaging (TDI), an emerging technique that measures velocities of the myocardium in systole and diastole, as a screening tool for these abnormalities.

## METHODS

**Study population.** We studied 49 obese children and adolescents from the patient population attending the Obesity Clinic for Children and Adolescents of the Antwerp University Hospital. Exclusion criteria were a significant concomitant illness, medication known to modify cardiac function and obvious clinical signs of cardiac disease. The control group consisted of 45 healthy volunteers, matched for age and sex. Patient characteristics are given in Table 1. The Antwerp University Hospital ethical review board approved the study. The participants and at least one of their parents provided written informed consent.

**Clinical assessment.** Each subject's height and body weight were measured. BMI was calculated using the formula (body weight in kilograms)/(body height in meters)<sup>2</sup> and BMI values were converted to SD scores (BMI-SDS) adjusted for age and sex using the updated British 1990 reference charts (14). Systolic (SBP) and diastolic blood pressure (DPB) was measured by the cuff method (Dinamap automated vital signs monitor, Criticon, Nordstedt, Germany). Hematological and biochemical variables were determined in the obese subjects from fasting blood samples and included glucose, insulin, total cholesterol, triglycerides (TG), and HDL (HDL) cholesterol. LDL (LDL) cholesterol and the QUICKI index, an index for insulin resistance

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**Abbreviations:** LV, left ventricle; LVM, left ventricular mass =  $\{1.04[(IVSd + LVIDD + LVPWd)^3 - (LVIDD)^3] - 13.6\text{ g}\}$

**Table 1.** Clinical characteristics of obese and nonobese subjects

	Nonobese	Obese	<i>p</i>
Number	45	49	
Sex (boys/girls)	22/23	22/27	0.698
Age (y)	11.5 ± 3.2	11.2 ± 2.8	0.645
BMI (kg/m <sup>2</sup> )	17.2 ± 2.9	28.3 ± 7.1	<0.001
BMI - SDS	-0.48 ± 1.11	2.84 ± 0.92	<0.001
BSA (m <sup>2</sup> )	1.30 ± 0.35	1.57 ± 0.33	<0.001
Systolic blood pressure (mm Hg)	115 ± 14	132 ± 14	<0.001
Diastolic blood pressure (mm Hg)	62 ± 9	72 ± 11	<0.001
Heart rate (bpm)	84 ± 15	79 ± 13	0.232
Total cholesterol (mg/dL)	—	166.4 ± 33.8	—
HDL-cholesterol (mg/dL)	—	47.9 ± 9.7	—
Triglycerides (mg/dL)	—	112.8 ± 107.8	—
LDL-cholesterol (mg/dL)	—	92.3 ± 32.3	—
Fasting glucose (mg/dL)	—	82.5 ± 6.2	—
Fasting insulin (μIU/mL)	—	17.0 ± 12.4	—
QUICKI index	—	0.331 ± 0.033	—

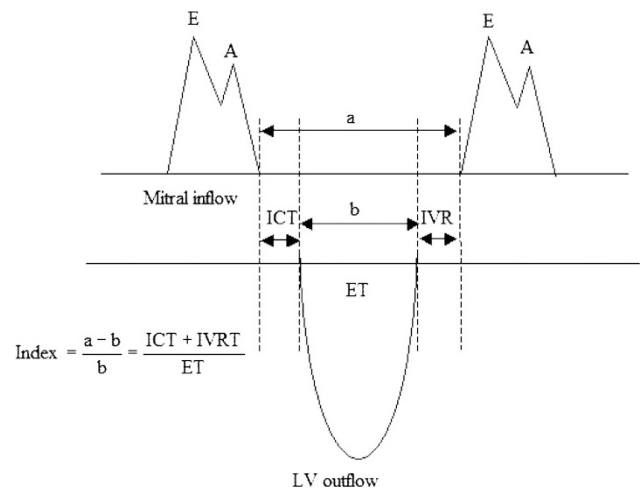
Values are expressed as mean (SD), significant values ( $p < 0.05$ ) are given in boldface.

BMI, body mass index; BMI-SDS, BMI standard deviation scores; BSA, body surface area; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

(15), were calculated using the formulas (LDL = total cholesterol - (TG/5) - HDL) and (QUICKI = 1/(log fasting insulin + log fasting glucose), respectively.

**Echocardiographic measurements.** After recording a standard 12 lead ECG (Mac 5000, GE, Marquette Medical Systems, Milwaukee, WI), a complete echocardiographic study with a simultaneous ECG (standard lead II) was performed on each patient and control subject using a Hewlett-Packard Sonos 5500, equipped with a S8 (3–8 MHz) transducer. Guided by two-dimensional echocardiography, standard M-mode recordings of the left ventricle (LV) dimensions and function were obtained. The LV mass (LVM) and relative posterior wall thickness were calculated according to the formulae of Devereux *et al.* (16). The methods of correcting LVM for body size have varied between studies. Left ventricular hypertrophy has been underestimated in the obese with the use of LVM divided by body surface area (BSA) because this index considers obesity as a physiologic variable. Height 2.7 (in meters) had been validated and recommended for indexing LVM (4) and was used in this study. Conventional Doppler tracings of the mitral and the tricuspid valve and pulmonary venous return flow were obtained from an apical 4-chamber view. The Doppler cursor line was placed in the inlet or the vein at an angle as parallel to flow as possible and in the position of maximal velocity. Doppler values of the aortic and pulmonary venous flow were measured from the suprasternal and parasternal short axis, respectively. Duration values were corrected for heart rate. Tissue Doppler values of the septal mitral annulus were obtained from the apical four-chamber view. The ratio of early mitral flow velocity (E-wave) to early diastolic velocity of the mitral annulus (E/E') was calculated. The Doppler-derived index of combined systolic and diastolic myocardial performance (Tei-index), defined as the sum of isovolumetric relaxation time and isovolumetric contraction time, divided by ejection time was used for quantification of the global right and left ventricular function (Fig. 1) (17). All Doppler signals were recorded at a speed of 50 mm/s. For each parameter, the average of three cycles was used. All the measurements were made off-line by the same observer blinded to the patients' clinical details.

**Statistical analysis.** Data are summarized using means and standard deviations, unless indicated otherwise. Means of obese and nonobese subjects were compared using an unpaired *t* test or Mann Whitney *U*-test, for categorical variables the  $\chi^2$  test was used. To investigate the relative influence of obesity versus associated cardiovascular risk factors (parameters of carbohydrate and lipid metabolism) on the echocardiographic variables that differed between obese and nonobese, linear regression analysis was performed. BMI-SDS, BSA, age, SBP, DBP, total cholesterol, HDL, LDL, TG, fasting glucose, fasting insulin, and the QUICKI index were *a priori* considered as possible determinants. Univariable regression models were constructed to examine the associations of predictor variables with the dependent echocardiographic variables (a *p* value of 0.10 was used here to indicate statistical significance). Stepwise multiple regression analysis was then used to determine which determinants independently explained a significant ( $p < 0.05$ ) fraction of the variance of the dependent variables. Residual analysis was performed to check the validity of model

**Figure 1.** Diagram of mitral inflow pattern, aortic outflow pattern, isovolumic time intervals and Tei-index.

assumptions. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., 2001, Chicago), version 11.0. A *p* value of  $\leq 0.05$  was considered statistically significant.

## RESULTS

**Clinical characteristics of the study groups.** The clinical, anthropometric, and metabolic characteristics of the study group are shown in Table 1. The obese and nonobese subjects were comparable with respect to age, sex, and heart rate. Obese subjects, however, had significantly higher z-scores for BMI, higher body surface area, and higher SBP and DBP (Table 1).

**LV dimensions and systolic function.** LV wall dimensions were higher in the obese population (Table 2). Statistical significance was reached for ventricular septum in systole and diastole (IVSs and IVSd), internal LV diameter in diastole (LVIDd), LV posterior wall in diastole and systole (LVPWd and LVPWs), relative posterior wall thickness and LVM and LVMI. The contractility indices (ejection fraction, fractional shortening, and velocity of circumferential shortening) were similar in obese and nonobese subjects (data not shown).

**Diastolic function.** For the conventional Doppler measurements, the maximal and mean velocities of active mitral filling ( $A_{max}$  and  $A_{mean}$ ) were similar in obese and normal subjects (Table 2). Tissue Doppler derived indices of the septal mitral annulus showed generally lower velocities in the obese population, although only significant for the E' wave velocity, resulting in a significant higher E/E' ratio. The pulmonary venous flow velocity during systole showed a trend to be higher in obese children ( $p = 0.058$ ).

**Time intervals and duration.** The Tei-index for the left ventricle was significantly lower in the obese subjects (Table 2). Tei-index for the right ventricle was difficult to obtain, because it was often impossible to simultaneously record the interval between cessation and onset of the tricuspid inflow and the right ventricular ejection time. The duration of the pulmonary venous flow during atrial contraction was significantly longer in obese subjects.

**Multiple regression analysis.** To investigate the relative influence of obesity *per se* versus the associated cardiovascular risk factors (parameters of carbohydrate and lipid metab-

**Table 2.** Comparison of left ventricular dimensions, diastolic function, and time intervals between obese and nonobese subjects

	Nonobese	Obese	<i>p</i>
LV dimensions			
IVSd (cm)	0.62 ± 0.12	0.69 ± 0.14	<b>0.012</b>
IVSs (cm)	0.97 ± 0.20	1.08 ± 0.20	<b>0.005</b>
LVIDd (cm)	4.43 ± 0.55	4.65 ± 0.41	<b>0.041</b>
LVIDs (cm)	2.81 ± 0.36	2.90 ± 0.32	0.217
LVPWd (cm)	0.47 ± 0.10	0.54 ± 0.08	<b>&lt;0.001</b>
LVPWs (cm)	0.93 ± 0.17	1.11 ± 0.18	<b>&lt;0.001</b>
LVM (g)	78.1 ± 39.3	99.7 ± 35.4	<b>0.008</b>
LVMI	24.9 ± 6.2	33.8 ± 10.7	<b>&lt;0.001</b>
RPWT	0.21 ± 0.04	0.23 ± 0.03	<b>0.005</b>
ESWS (g/cm <sup>2</sup> )	90.1 ± 20.6	84.7 ± 17.3	0.199
Diastolic function			
Mitral valve			
A <sub>max</sub> (m/s)	0.43 ± 0.10	0.42 ± 0.08	0.706
A <sub>mean</sub> (m/s)	0.26 ± 0.06	0.26 ± 0.05	0.540
E/A <sub>max</sub>	2.29 ± 0.56	2.40 ± 0.48	0.323
E/A <sub>mean</sub>	2.14 ± 0.43	2.22 ± 0.45	0.431
Mitral valve tissue			
Doppler imaging			
E' (m/s)	0.14 ± 0.02	0.12 ± 0.02	<b>&lt;0.001</b>
E/E' (m/s)	6.71 ± 1.22	8.11 ± 1.30	<b>&lt;0.001</b>
Pulmonary venous flow			
PVS (m/s)	0.47 ± 0.08	0.51 ± 0.10	0.058
PVD (m/s)	0.56 ± 0.09	0.56 ± 0.10	0.951
D/S	1.19 ± 0.17	1.12 ± 0.24	0.126
TIME intervals			
TEI-index (left ventricle)	0.40 ± 0.06	0.37 ± 0.06	<b>0.005</b>
IVRT (ms)	54 ± 9	53 ± 9	0.519
PVA <sub>dur</sub> (ms)	97 ± 20	107 ± 17	<b>0.032</b>

Values are expressed as mean (SD), significant values (*p* < 0.05) are given in boldface.

A<sub>max</sub>, maximum velocity of active mitral filling; A<sub>mean</sub>, mean velocity of active mitral filling; E, velocity of passive mitral filling; ESWS, left ventricular end-systolic meridional wall stress; IVRT, isovolumetric relaxation time; IVSs, ventricular septum in systole; IVSd, ventricular septum in diastole; LVIDd, internal LV diameter in diastole; LVIDs, internal LV diameter in systole; LVM, left ventricular mass; LVMI, left ventricular mass index; LVPWd, LV posterior wall in diastole; LVPWs, LV posterior wall in systole; PVA<sub>dur</sub>, time of pulmonary venous flow during atrial filling; PVD, pulmonary venous flow velocity during diastole; PVS, pulmonary venous flow velocity during systole; RPWT, relative posterior wall thickness; TDI E', myocardial velocity during early filling using tissue Doppler imaging.

olism) on the echocardiographic variables that differed between obese and nonobese, stepwise multiple regression analysis was performed. Mainly BMI-SDS and/or BSA had an independent effect on the echocardiographic variables that differed between obese and nonobese subjects (Table 3). The associated metabolic risk factors, more specifically fasting glucose, insulin, total cholesterol, TG, HDL cholesterol, LDL cholesterol, and the QUICKI index, did not explain a significant proportion of the variance of echocardiographic variables.

## DISCUSSION

This cross-sectional study provides evidence that asymptomatic obese children already exhibit abnormalities of left ventricle structure and function (consisting of increased left ventricular wall dimensions and mass and alteration of dia-

stolic function) that can be detected by TDI. Furthermore, BMI-SDS and/or BSA and not the associated cardiovascular risk factors (parameters of carbohydrate and lipid metabolism) were found to be independent predictors of adverse LV remodeling and of diastolic dysfunction. To our knowledge, this is the first study that evaluates early echocardiographic signs (including TDI) of subclinical cardiac dysfunction in obese children and adolescents and the respective influence of obesity *per se versus* the associated cardiovascular risk factors.

**LV morphology and systolic function.** The association of LV remodeling and obesity in the present study is supported by previous studies in adults and children (18–20). The Bogulosa Heart Study showed a strong association between LVM in childhood and the degree of obesity (18). In the Strong Heart Study, increased levels of LVM were found in overweight and obese adolescents. Additionally, they found a significant increase in stroke volume in obese adolescents, indicating increased cardiac workload (20). In the present study, no patient presented with subclinical systolic dysfunction. Most echo-cardiographic studies that assessed systolic function in obese subjects have shown normal results (21–23). Reduction of indices of systolic function were only found in patients with a considerable degree of obesity, suggesting that left ventricular function is affected late in the course of obesity (20,24).

**Diastolic function.** The Doppler method of measuring indices of left ventricular filling has been shown to be of great value in assessing diastolic function. However, when volume overload is present, as it is in obesity, normal values may result as the increase in left atrial pressure caused by intravascular volume can mask alterations observed in the early phases of abnormal diastolic relaxation. TDI is an emerging technique that modifies conventional Doppler to measure the velocity of the myocardium in systole and diastole. It has proved to be more sensitive to detect subclinical LV dysfunction in several disorders with normal standard parameters of global LV systolic function (25,26). Few studies have investigated diastolic function in obese children and adolescents. Harada *et al.* (27) found altered transmitral and pulmonary venous velocities in 21 obese children using pulse-wave Doppler, suggesting a reduction in early diastolic filling. In the present study, we did not find these abnormalities. Only one recent study investigated diastolic function using TDI in 25 obese and overweight children (28) providing unique insights into the effects obesity on LV diastolic function. They observed impaired early diastolic function (E') in the overweight and obese group. The E'/A' ratio was found to be inversely related to BMI. In the present study, we confirmed these results in a larger group of 49 young obese subjects. The relation between obesity and diastolic filling is not well understood. Although the association of myocardial fatty infiltration with obesity is well recognized, it is not a prominent finding at autopsy. Altered loading conditions are also likely to contribute. Elevated preload is to be expected in obese patients, which would indicate early filling. It has been reported to have a marked effect on peak velocity during atrial contraction and reversal flow of pulmonary venous flow with less effect on pulmonary diastolic flow velocity.

**Table 3.** Respective influence of obesity vs other variables of the metabolic syndrome: stepwise multivariate linear regression analysis

Dependent variable	R <sup>2</sup>	Constant	β-coefficient	Significant predictors (p)
<b>LV dimensions</b>				
IVSs (cm)	0.716	0.433	0.409	BSA (<0.001)
IVSd (cm)	0.508	0.344	0.210	BSA (0.003)
LVIDd (cm)	0.760	3.035	1.045	BSA (<0.001)
LVPWd (cm)	0.648	0.255	0.180	BSA (<0.001)
LVPWs (cm)	0.565	0.554	0.353	BSA (<0.001)
LVM (g)	0.758	-14.101	136.99	BSA (<0.001)
			-9.285	Age (0.008)
LVMI	0.637	25.593	3.303	BMI-SDS (<0.001)
RPWT	0.487	0.132	0.005	BMI-SDS (0.039)
			0.001	BP Syst (0.009)
<b>Diastolic function</b>				
Mitral valve TDI: E' (m/s)	0.441	0.138	-0.005	BMI-SDS (<0.001)
Mitral valve TDI: E/E' (m/s)	0.446	6.967	0.317	BMI-SDS (<0.001)
Pulmonary venous flow: PVS (m/s)	0.369	55.861	1.335	BMI-SDS (0.016)
			-0.742	Age (0.040)
<b>Time intervals</b>				
TEI-index (left ventricle)	0.330	0.342	-0.008	BMI-SDS (0.018)
			-0.005	Age (0.041)
PVA <sub>dur</sub> (ms)	0.378	75.270	19.910	BSA (0.043)

BMI-SDS, BMI standard deviation scores; BSA, body surface area; D, pulmonary venous flow velocity during diastole; E, velocity of passive mitral filling; IVSs, ventricular septum in systole; IVSd, ventricular septum in diastole; LVIDd, internal LV diameter in diastole; LVM, left ventricular mass; LVMI, left ventricular mass index; LVPWd, LV posterior wall in diastole; LVPWs, LV posterior wall in systole; PVA<sub>dur</sub>, time of pulmonary venous flow during atrial filling; PVS, pulmonary venous flow velocity during systole; RPWT, relative posterior wall thickness; TDI E', myocardial velocity during early filling using tissue Doppler imaging.

**Influence of associated cardiovascular risk factors.** Obesity is associated with a group of metabolic abnormalities [e.g., dyslipidemia (8), insulin resistance (9), hyperglycaemia), and hypertension (10)], referred to as the “metabolic syndrome.” It has been suggested that the metabolic abnormalities could be involved in the modulation of left ventricular structure. Several studies have investigated the relation between insulin resistance and left ventricular mass on both obese and hypertensive subjects with varying results. Some studies found a relation between insulin resistance and left ventricular mass (29,30), whereas others found no relation at all after adjusting for covariates. In the present study, the associated cardiovascular risk factors (more in specific parameters of carbohydrate and lipid metabolism) did not predict a significant portion of adverse LV remodelling and of diastolic dysfunction when adjusted for obesity.

**Limitations.** There are some limitations to consider in the interpretation of our results. The current study was cross-sectional in design; therefore, temporal associations between obesity, blood pressure elevation, metabolic factors, and cardiac structure and function could not be evaluated. Follow-up studies should be helpful in elucidating the cause-and-effect relations and the underlying mechanism. In addition, there may be selection bias toward children with increased morbidity as this is a referral population.

In conclusion, this study has demonstrated that young, obese children and adolescents have significant changes in left ventricular wall dimensions and early diastolic filling compared with nonobese subjects. Obesity *per se* and not the associated cardiovascular risk factors (parameters of carbohydrate and lipid metabolism) predicted the early cardiac abnormalities. TDI proved to have additional value in the evaluation of ventricular filling in this population.

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