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Childhood Obesity

Impact on Cardiac Geometry and Function

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ABSTRACT

OBJECTIVES The aim of our study was to assess geometric and functional changes of the heart in obese compared with nonobese children and adolescents.

BACKGROUND Obesity in children and adolescents has increased over the past decades and is considered a strong risk factor for future cardiovascular morbidity and mortality. Obesity has been associated with myocardial structural alterations that may influence cardiac mechanics.

METHODS We prospectively recruited 61 obese (13.5 ± 2.7 years of age, 46% male sex, SD score body mass index, 2.52 ± 0.60) and 40 nonobese (14.1 ± 2.8 years of age, 50% male sex, SD score body mass index, −0.33 ± 0.83) consecutive, nonselected Caucasian children and adolescents. A standardized 2-dimensional (2D) echocardiography and 2D speckle-tracking analysis was performed in all children. Furthermore, blood chemistry including lipid and glucose metabolism was assessed in all children.

RESULTS Compared with nonobese children, blood pressure, low-density lipoprotein cholesterol, and parameters of glucose metabolism were significantly increased in obese children, whereas high-density lipoprotein cholesterol was significantly lower. Compared with nonobese children, obese children were characterized by enlarged left- and right-sided cardiac chambers, thicker left ventricular walls, and, consequently, increased left ventricular mass. Despite a comparable left ventricular ejection fraction, decreased tissue Doppler–derived peak systolic velocity and regional basoseptal strain were found in obese children compared with nonobese children. Beyond that, 2D speckle tracking–derived longitudinal (−18.2 ± 2.0 vs. −20.5 ± 2.3, $p < 0.001$) and circumferential (−17.0 ± 2.7 vs. −19.5 ± 2.9, $p < 0.001$) strain of the left ventricle was reduced in obese children compared with nonobese children. Diastolic function was also impaired in obese compared with nonobese children. Both longitudinal strain and circumferential strain were independently associated with obesity.

CONCLUSIONS The results of this study demonstrate that childhood obesity is associated with significant changes in myocardial geometry and function, indicating an early onset of potentially unfavorable alterations in the myocardium. (J Am Coll Cardiol Img 2014;7:1198–205) © 2014 by the American College of Cardiology Foundation.

In the 1980s and 1990s, the prevalence of obesity increased dramatically in children and adolescents (1,2) and has plateaued in the past years at a disturbingly high level (3,4) to become a major health problem. Obesity has been associated with heart failure (5), left ventricular (LV) dilation, increased LV wall stress, and compensatory LV hypertrophy in adults (6). However, it has become clear

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that many of these abnormalities may already occur in childhood and adolescence (1,7–11).

Nevertheless, the association between isolated obesity and cardiovascular risk has been difficult to assess because obesity itself is highly associated with cardiovascular risk factors such as arterial hypertension, impaired glucose tolerance, diabetes mellitus, and dyslipidemias. Hence, the results have been controversial with regard to the role of obesity per se (12–15).

For this reason, children are likely to be the ideal candidates for providing insight into the myocardial changes related to obesity because they are suggested to be free of other cardiovascular risk factors in different echocardiographic studies (7,8,10). However, numerous studies have shown that a high body mass index (BMI) or other measures of obesity in children and adolescents are associated with adverse levels of lipids/lipoproteins and blood pressure and are related to insulin resistance (16,17). The value of the aforementioned echocardiographic studies is limited due to the lack of metabolic data in the control group (7,8,10,18) and the sole use of tissue Doppler imaging (TDI) for LV deformation analysis (7).

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The aim of our study, therefore, was to assess geometric and functional alterations in obese compared with nonobese children and adolescents when blood pressure, glucose metabolism, and lipid levels were accounted for in both groups.

METHODS

STUDY POPULATION. We prospectively recruited 61 overweight and obese and 40 nonobese consecutive Caucasian children and adolescents from the previously described Leipzig Atherobesity Childhood cohort (19). The children and adolescents were 8 to 21 years of age, free of known diseases, and not taking any medication. All subjects were characterized using anthropometric parameters, measures of glucose and insulin metabolism, and cardiovascular risk, as described recently (19,20). To determine insulin resistance, homeostatic model assessment insulin resistance (HOMA-IR) was calculated. The HOMA model (21) is a structural computer model of the glucose insulin feedback system in the homeostatic (overnight-fasted) state calculated from fasting plasma glucose and insulin concentrations.

The BMI was standardized to age- and sex-specific percentiles applying German reference data (22) and is given as the BMI standard deviation score (BMI-SDS), which is a measure of relative weight adjusted for child age and sex. Cutoffs of 1.28 SD score (90th percentile) and 1.88 SD score (97th percentile) were defined as overweight and obese, respectively. Written informed consent was obtained from all parents and from children older than 12 years of age. The study was approved by the local ethics committee (registration no. 029-2006).

ECHOCARDIOGRAPHY. Every subject underwent a standardized 2-dimensional (2D) echocardiography examination using a commercial ultrasound system (Vivid 7, GE Health Medical, Milwaukee, Wisconsin). All images were recorded using harmonic imaging and stored digitally for analysis. 2D images were recorded using a temporal resolution of at least 60 frames/s; TDI frames were recorded at a rate of >100 frames/s. All data were read and analyzed by investigators who were blinded to conditions.

Chamber quantification and calculation of parameters of global LV systolic function followed current standards and, if applicable, were also indexed to body height raised to a power of 2.7 (23). Furthermore, *z*-scores of LV dimensions and LV mass were calculated on the basis of normal values of M-mode measurements (24,25). Of note, 7 obese children could not be included in the *z*-score analysis for interventricular septum diastolic (IVSd), posterior wall diastolic (PWd), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) due to a body surface area >2.25 cm^2. For those children, the *z*-score is not validated according to national reference values (25). Deformation analysis of the left ventricle using TDI and 2D speckle-tracking echocardiography (2D-STE) was performed using EchoPac PC software version 113 (GE Health Medical) and according to a recent consensus statement (26). Analysis of diastolic function was also performed according to current guidelines (27).

For correlation analysis, endothelial function was evaluated by measuring the reactive hyperemia index using the EndoPat-Device (Itamar Medical Ltd., Caesarea, Israel), and intima media thickness of the left and right common carotid arteries were recorded.

STATISTICAL ANALYSIS. Statistical analysis was carried out using SPSS version 20 (IBM, Chicago, Illinois). Quantitative data are expressed as mean ± SD and qualitative data as absolute number (%). Comparisons between the groups were made with the Pearson chi-square test for categorical variables and 2-tailed Student *t* test for continuous variables. When continuous variables were not normally distributed

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

2D-STE = 2-dimensional speckle-tracking echocardiography

3D = 3-dimensional

BMI-SDS = body mass index standard deviation score

CI = confidence interval

HDL = high-density lipoprotein

HOMA-IR = homeostatic model assessment insulin resistance

ICC = intraclass correlation

IVSd = interventricular septal thickness at diastole

LA = left atrial

LV = left ventricular

LVEDD = left ventricular end-diastolic diameter

PWd = posterior wall at diastole

TDI = tissue Doppler imaging

TABLE 1 Baseline Characteristics

	Nonobese (n = 40)	Obese (n = 61)	p Value
Age, yrs	14.1 ± 2.8	13.5 ± 2.7	0.29
Male	20 (50.0)	28 (45.9)	0.69
Height, m	1.65 ± 0.1	1.66 ± 0.1	0.86
Body mass, kg	52.7 ± 14.0	85.7 ± 20.8	<0.001
BMI, kg/m^2	19.0 ± 2.6	30.8 ± 5.3	<0.001
BMI-SDS	−0.33 ± 0.83	2.52 ± 0.60	<0.001
Waist circumference, cm	67.0 ± 7.3	91.8 ± 11.9	<0.001
Heart rate, beats/min	70 ± 12	72 ± 10	0.19
SBP, mm Hg	107 ± 12	117 ± 11	<0.01
DBP, mm Hg	59 ± 8	63 ± 7	<0.01
Triglycerides, mmol/l	0.83 ± 0.4	1.2 ± 0.7	0.001
Total cholesterol, mmol/l	3.8 ± 0.8	4.3 ± 0.8	0.02
LDL cholesterol, mmol/l	1.96 ± 0.6	2.35 ± 0.7	<0.01
HDL cholesterol, mmol/l	1.34 ± 0.3	1.20 ± 0.3	0.02
Fasting glucose, mmol/l	4.5 ± 0.5	4.7 ± 0.6	0.047
Fasting insulin, pmol/l	65.3 ± 27.3	125.8 ± 61.0	<0.001
HOMA-IR	1.9 ± 0.8	3.8 ± 1.9	<0.001

Values are mean ± SD or n (%).

BMI = body mass index; BMI-SDS = body mass index SD score; DBP = diastolic blood pressure; HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment insulin resistance; LDL = low-density lipoprotein; SBP = systolic blood pressure.

or the variance was not equal, the Kruskal-Wallis nonparametric test was used. Correlation analyses were performed using the Pearson correlation. To evaluate the independent influence of obesity on echocardiographic parameters, a stepwise multiple linear regression analysis was performed using longitudinal strain and circumferential strain as dependent variables. Independent variables included those showing a p value <0.01 on univariate analysis. Interobserver and intraobserver reproducibility was evaluated by means of the intraclass correlation coefficient (ICC). Differences were considered statistically significant when a p value <0.05 was obtained.

RESULTS

BASELINE CHARACTERISTICS. The main clinical and metabolic data of obese and nonobese children and adolescents are shown in **Table 1**. The subjects were well matched ($p > 0.05$) with regard to age, sex distribution, and body height. Statistically significant differences were found in all parameters related to body mass (BMI, BMI-SDS, and waist circumference). Furthermore, blood pressure and lipid and glucose metabolism parameters were significantly different between both groups.

CARDIAC GEOMETRY. Echocardiographic variables of myocardial geometry and global systolic LV function are summarized in **Table 2**. Compared with the nonobese group, obese children and adolescents were characterized by both thicker LV walls (IVSd and PWd by 18%, $p < 0.001$) and LV chamber dimensions (2D LV end-diastolic volume by 29%, $p < 0.001$). Consequently, calculated LV mass and LV mass index were ~40% higher in obese children compared with nonobese subjects ($p < 0.001$). Furthermore, left atrial (LA) volume, LA volume index, right atrial area, and right ventricular diameter were also enlarged in obese compared with nonobese subjects ($p < 0.001$).

To control for physiological increase in geometric parameters with physiological development and growth, all the above-mentioned measurements were indexed to the 2.7 power of height (Online Table 1). Higher values indexed to the 2.7 power of height were found for IVSd, PWd, 2D LV end-diastolic volume, LA diameter, right atrial area, and right ventricular diameter in obese children compared with lean controls. However, indexed LV diameters (diastolic and systolic) were comparable between both groups. Interestingly, *z*-scores for LVEDD and LV end-systolic dimension were significantly lower in obese children with a higher proportion of obese children below the 5th percentile for LVEDD (18.5% vs. 0.0%, $p < 0.01$). In contrast, *z*-scores for LV mass were significantly higher in obese children with a higher proportion of obese children above the 95th percentile (14.8 vs. 0.0%, $p < 0.001$), which is defined as a threshold for LV hypertrophy in children (24). Using the older LV mass index cutoff >38.6 g/m$^{2.7}$ (28), even more obese children would have received a diagnosis of LV hypertrophy (47.5% vs. 10.0%, $p < 0.001$). These findings translated into a significantly higher relative wall thickness in obese children, indicating a concentric remodeling ($p < 0.01$).

Moreover, *z*-scores for LA diameter were significantly higher in obese children compared with lean controls ($p < 0.001$) with a significantly higher proportion of obese children above the 95th percentile (33.3% vs. 10.0%, $p < 0.01$).

SYSTOLIC LV FUNCTION, TDI, AND 2D-STE. There was no difference in global LV ejection fraction between the 2 studied groups; however, there were higher values of calculated absolute and indexed stroke volume and cardiac output in the obese group (**Table 2**, Online Table 1).

The results derived from TDI and 2D-STE are summarized in **Table 3**. Tissue Doppler-derived peak systolic velocity, averaged from the values measured at the septal, lateral, anterior, inferior, posterior, and anteroseptal mitral annulus, was reduced in obese compared with nonobese children ($p < 0.001$). Also regional deformation in the basoseptal region was reduced in obese children ($p < 0.001$). Given the

disadvantages of TDI, we evaluated longitudinal, circumferential, and radial deformation properties of the left ventricle using 2D-STE (Table 3, Figure 1). Two children in the nonobese group and 3 in the obese group were excluded from the 2D-STE analysis due to poor acoustic window.

Average longitudinal LV strain, strain rate, and displacement, which are all measures of longitudinal function, were significantly reduced in obese compared with nonobese children and adolescents ($p < 0.001$ for all comparisons).

Average LV circumferential strain was also significantly blunted in obese compared with nonobese children ($p < 0.001$), whereas the average LV circumferential strain rate did not differ significantly between the groups ($p = 0.067$).

Radial function was not significantly different between groups.

DIASTOLIC LV FUNCTION. Mitral E- to mitral A-wave peak velocity was reduced in obese children ($p = 0.001$) (Table 4). Furthermore, septal and lateral mitral annulus TDI peak E-wave velocity was reduced in obese compared with nonobese children and adolescents ($p < 0.001$ and $p = 0.004$). Consequently, the values of E/E′, both at the septal and lateral mitral annulus, were increased in the obese compared with nonobese group ($p < 0.001$ and $p = 0.001$).

UNIVARIATE AND MULTIVARIATE CORRELATION ANALYSES. The univariate correlation analysis is summarized in Table 5. Several clinical, echocardiographic, and metabolic parameters were related to BMI-SDS, longitudinal strain, and circumferential strain in the univariate analysis. In a stepwise multiple regression analysis, longitudinal strain was independently associated with BMI-SDS and HDL cholesterol, whereas circumferential strain was solely linked with BMI-SDS (Table 6).

INTEROBSERVER AND INTRAOBSERVER REPRODUCIBILITY. Interobserver agreement as assessed by the ICC was 0.92 (95% confidence interval [CI]: 0.70 to 0.98), 0.83 (95% CI: 0.34 to 0.96), and 0.94 (95% CI: 0.76 to 0.98) for longitudinal, circumferential, and radial strain, respectively. Similar results were obtained for intraobserver agreement: the ICC was 0.98 (95% CI: 0.91 to 0.99), 0.85 (95% CI: 0.43 to 0.96), and 0.91 (95% CI: 0.65 to 0.98) for longitudinal, circumferential, and radial strain, respectively.

DISCUSSION

The present study demonstrates that childhood obesity, compared with an age-matched nonobese control group, is independently associated with significant changes in myocardial geometry and function.

TABLE 2 Echocardiographic Findings: Geometry and Global Left Ventricular Function

	Nonobese (n = 40)	Obese (n = 61)	p Value
Left ventricle			
IVSd, cm	0.82 ± 0.14	0.97 ± 0.13	<0.001
PWd, cm	0.78 ± 0.13	0.92 ± 0.16	<0.001
LVEDD, cm	4.5 ± 0.5	4.7 ± 0.5	<0.01
LVESD, cm	2.9 ± 0.3	3.0 ± 0.4	0.05
FS, %	35.0 ± 3.6	36.0 ± 5.2	0.65
LVM, g	113.0 ± 38.7	157.7 ± 43.8	<0.001
LVMI, g/m$^{2.7}$	28.7 ± 6.7	40.0 ± 9.2	<0.001
2D-LVEDV, ml	85.1 ± 21.7	109.6 ± 25.2	<0.001
2D-LVESV, ml	31.2 ± 8.9	40.9 ± 10.8	<0.01
LVEF, %	63.4 ± 4.8	62.6 ± 5.0	0.4
SV, ml	53.9 ± 13.9	68.7 ± 17.1	<0.001
CO, l/min	3.7 ± 0.9	4.9 ± 1.3	<0.001
Left atrium			
LA diameter, cm	2.86 ± 0.33	3.61 ± 0.732	<0.001
LAV, ml	35.8 ± 9.9	48.7 ± 11.8	<0.001
LAVI, ml/m$^{2.7}$	9.2 ± 2.6	12.5 ± 2.4	<0.001
Right atrial area, cm^2	10.7 ± 2.4	12.8 ± 2.4	<0.001
Right ventricular diameter, cm	2.2 ± 0.4	2.5 ± 0.4	<0.001

Values are mean ± SD.

CO = cardiac output; 2D-LVEDV = 2-dimensional left ventricular end-diastolic volume; 2D-LVESV = 2-dimensional left ventricular end-systolic volume; FS = fractional shortening; IVSd = interventricular septum diastolic; LA = left atrial; LAV = left atrial volume; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVM = left ventricular mass; LVMI = left ventricular mass index; PWd = posterior wall diastolic; SV = stroke volume.

SYSTOLIC FUNCTION OF THE LEFT VENTRICLE. When evaluating systolic function of the left ventricle, the global ejection fraction was found to be normal and did not differ between groups. However, sophisticated imaging modalities allow the

TABLE 3 Tissue Doppler and Speckle Tracking–Derived Left Ventricular Systolic Function

	Nonobese	Obese	p Value
TDI	40	61	
Average S′, cm/s	7.2 ± 1.1	6.6 ± 1.0	<0.001
Basoseptal strain, %	−22.4 ± 4.0	−18.7 ± 4.0	<0.001
2D-STE	38	58	
2D-STE, longitudinal function			
Average longitudinal strain, %	−20.5 ± 2.3	−18.2 ± 2.0	<0.001
Average longitudinal strain rate, s^{-1}	−1.28 ± 0.17	−1.11 ± 0.13	<0.001
Average longitudinal displacement, mm	−9.5 ± 1.3	−8.1 ± 1.5	<0.001
2D-STE, circumferential function			
Average circumferential strain, %	−19.5 ± 2.9	−17.0 ± 2.7	<0.001
Average circumferential strain rate, s^{-1}	−1.61 ± 0.20	−1.53 ± 0.22	0.067
2D-STE, radial function			
Average radial strain, %	43.3 ± 14.6	38.6 ± 10.1	0.09
Average radial strain rate, s^{-1}	1.85 ± 0.36	1.85 ± 0.39	0.99
Average radial displacement, mm	5.7 ± 1.1	5.5 ± 1.0	0.32

Values are n or mean ± SD.

S′ = average peak systolic velocity measured at six points of the left ventricle; other abbreviations as in Table 1.

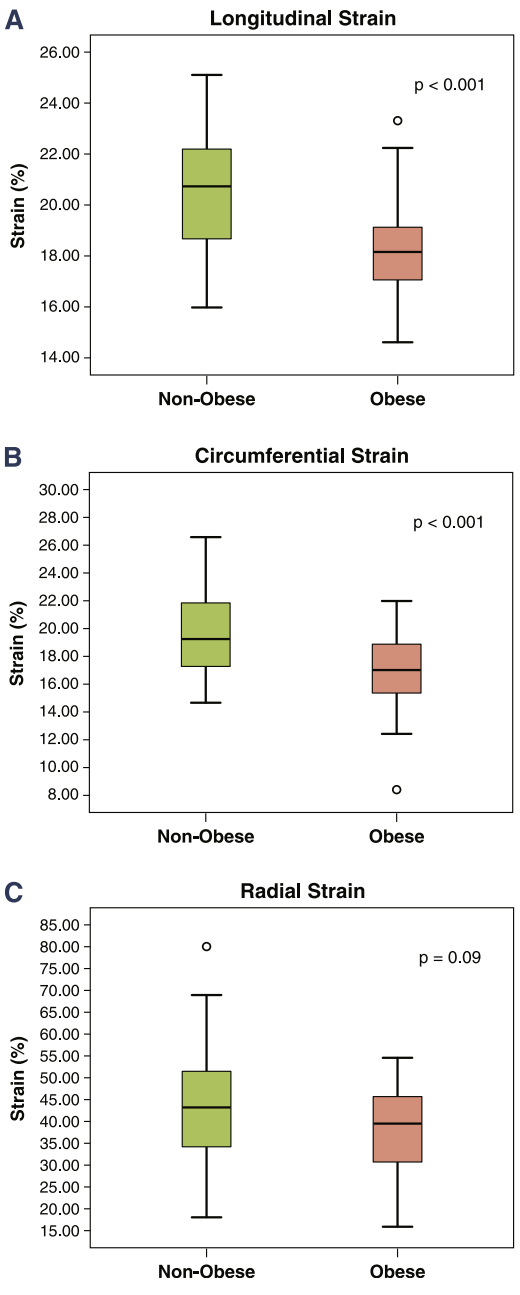

FIGURE 1 Strain Parameters in Nonobese and Obese Subjects

Longitudinal **(A)** and circumferential strain **(B)** are reduced in obese children and adolescents compared with nonobese, whereas there is no significant difference with regard to radial strain **(C)**.

analysis of cardiac mechanics beyond global ejection fraction. The 2 most important techniques are TDI and speckle tracking, either 2D or even 3-dimensional (3D). Our data derived from TDI, which demonstrated a reduced myocardial velocity and regional deformation properties in obese children are consistent with data from other studies describing a reduced longitudinal strain in obese children without increased blood pressure (7). Furthermore, the same patterns were observed in young obese adults in whom only TDI or 2D strain was able to identify subclinical LV dysfunction (29,30) The major criticism of TDI, however, has been the directional bias of the technology (26).

Therefore, we performed a 2D speckle tracking analysis, a technique associated with lower interobserver variability than TDI (26). We found a reduced longitudinal and circumferential strain in obese compared with nonobese children, whereas radial strain was comparable between groups. These results confirm those derived from TDI in obese children (7) and adults (29-31). Furthermore, our data are completely in line with those recently reported by Labombarda et al. (8), who showed reduced longitudinal and circumferential strain values and comparable radial strain values in obese and nonobese children. Yet, a recent study by Saltijeral et al. (10), using the novel technique of 3D wall motion tracking, was able to show reduced longitudinal and circumferential deformation properties, whereas radial strain was increased in obese compared with nonobese children. They interpreted this finding as a possible compensation mechanism to maintain global contractility at an early stage of obesity cardiomyopathy. In contrast, our data and those of others (8) show at least a trend toward lower radial strain values in the obese groups. Hypothetically, this difference might be due to the diverse techniques (2D- vs. 3D-derived strain analysis), which were used to assess radial strain. There are theoretical reasons why 3D-derived strain could be advantageous. In particular, out-of-plane motion limitation as the heart moves in and out of the imaging plane during the systole and diastole is not recognized in 2D echocardiography. However, to obtain reliable strain information, a frame rate >40 frames/s is required (32). Such a 3D frame rate or volume rate is currently not feasible, and Saltijeral et al. (10) reported that they used a rate of 17 to 22 volumes/s. A comparison of both 2D and 3D strain analysis in the same cohort would be helpful to determine the impact of the various techniques.

The fact, however, that the above-mentioned results obtained with several different techniques including TDI, 2D- and 3D-STE agree with each other (at least for longitudinal and circumferential strain), supports the biological plausibility of the findings. Changes in LV longitudinal strain have also been observed in children treated with anthracyclines due

TABLE 4 Diastolic Function of the Left Ventricle

	Nonobese (n = 40)	Obese (n = 61)	p Value
E/A	2.34 ± 0.58	1.96 ± 0.51	0.001
DT, ms	170 ± 21	173 ± 25	0.53
IVRT, ms	69 ± 11	74 ± 13	0.068
E′ lateral, m/s	0.20 ± 0.02	0.18 ± 0.03	0.004
E/E′ lateral	4.8 ± 0.9	5.5 ± 1.1	0.001
E′ septal, m/s	0.15 ± 0.02	0.13 ± 0.02	<0.001
E/E′ septal	6.3 ± 1.1	8.0 ± 1.7	<0.001

Values are mean ± SD.

DT = deceleration time; E′ = lateral or septal mitral annulus tissue Doppler imaging peak E-wave velocity; E/A = ratio of mitral E- to mitral A-wave peak velocity; E/E′ = lateral and septal, ratio of mitral E-wave peak velocity to lateral or septal mitral annulus tissue Doppler imaging peak E-wave velocity; IVRT = isovolumetric relaxation time.

TABLE 5 Univariate Linear Correlation Coefficients

	BMI-SDS	Average Longitudinal Strain	Average Circumferential Strain
BMI-SDS	NA	−0.51*	−0.46*
SBP	0.51*	−0.35*	−0.25†
LVMI	0.59*	−0.35*	−0.39*
LV-EDVI	0.56*	−0.39*	−0.27†
LAVI	0.59*	0.02‡	−0.20‡
E′ septal	−0.58*	0.38*	0.28*
Average longitudinal strain	−0.51*	NA	0.57*
Average longitudinal strain rate	−0.54*	NA	0.49*
Average circumferential strain	−0.46*	0.57*	NA
Triglycerides	0.33*	−0.36*	−0.26†
Total cholesterol	0.29*	−0.16‡	−0.08‡
LDL cholesterol	0.34*	−0.25†	−0.13‡
HDL cholesterol	−0.22†	0.39*	0.26†
HOMA-IR	0.66*	−0.44*	−0.35*
IMT	0.57*	−0.31*	−0.26†
RHI	−0.54*	0.30*	0.23†

Values are r = univariate correlation coefficients. *p < 0.01. †p < 0.05. ‡Not significant.

IMT = intima-media-thickness; NA = not available; RHI = reactive hyperemia index; other abbreviations as in Tables 1 and 2.

to acute lymphoblastic leukemia (33) or other pathological entities affecting the subendocardial layer such as hypertrophic, ischemic, and diabetic cardiomyopathy in adults (34).

CARDIAC GEOMETRY AND DIASTOLIC FUNCTION OF THE LEFT VENTRICLE. The morphological results of our study confirm previous data describing an increase in LV size/mass and LA volume in obese adults (5,6) and children or adolescents (6–9). Furthermore, we add information about the proportion of subjects above and below the 95th and 5th percentiles, respectively. These values are thought to define specific conditions (e.g., LV hypertrophy or LA dilation) (24,28). A significantly higher number of obese subjects were found above the 95th percentile for LV mass and LA size. Obesity leads to a higher total blood volume, cardiac output, and cardiac workload as well as higher peripheral resistance (6). Due to increased filling, the pressure and volume increases lead to dilation of cardiac chambers (6). It is proven that LV dilation and LV hypertrophy as well as LA enlargement are associated with adverse cardiac events and worse prognosis (35). Furthermore, increased LA size is also a feature of impaired diastolic function of the left ventricle. Measurement of LA volume is recommended for assessing diastolic dysfunction in adult patients (27). Our study describes decreased diastolic function in obese children, as indicated by a reduced E/A ratio, reduced annulus TDI peak E-wave velocities (E′) and increased E/E′ ratios. There were no significant differences with regard to deceleration or isovolumetric relaxation time. With respect to E′ and E/E′, our results are in agreement with those of previous studies (7,10). However, the present evidence remains inconclusive regarding E/A ratio and relaxation times. There are studies showing significant differences in E/A ratio but not the relaxation parameters (36) and vice versa (7). This might be due to low reproducibility, in particular for isovolumetric relaxation time (37).

POTENTIAL MECHANISM. In the obese group, systolic and diastolic blood pressures were significantly higher than in nonobese children. Although the measured blood pressure was still within normal limits in the obese group (38), higher blood pressure may affect myocardial deformation changes. In a stepwise multiple linear regression analysis including blood pressure, however, obesity remained the major independent factor associated with reduced longitudinal and circumferential strain.

It is described that the relationship between obesity and congestive heart failure could be mediated by insulin resistance (39). In our study, the obese children were already characterized by peripheral insulin resistance, as indicated by a mean HOMA-IR of 3.8. However, longitudinal and circumferential strain is only correlated with HOMA-IR on univariate analysis. Therefore, other explanations or confounding factors for disturbed systolic cardiac mechanics

TABLE 6 Multivariate Stepwise Regression Analysis

	Longitudinal Strain		Circumferential Strain	
	Beta	p Value	Beta	p Value
BMI-SDS	−0.450	<0.001	−0.456	<0.001
HDL cholesterol	0.307	0.001	–	–

Abbreviations as in Table 1.

may account for the findings. Insulin acts as a growth factor (40) and stimulates the sympathetic nervous system with an increased pressor reaction to angiotensin II (41), leading to hypertension, hypertrophy, and fibrosis in the myocardium (42). Furthermore, hyperinsulinemia leads to sodium retention and may thereby aggravate hypervolemia (43), which causes increased filling pressures and chamber dilation.

Interestingly, HDL cholesterol was independently associated with longitudinal strain in the stepwise multiple linear regression analysis. In diabetic cardiomyopathy, HDL cholesterol indirectly affects cardiac structure and function via its influence on metabolic triggers like hyperinsulinemia, hyperglycemia, and hyperlipidemia. Beyond the indirect mechanisms, HDL cholesterol also has direct influence on cardiac cellular structure and function via its anti-inflammatory, antioxidative, antifibrotic, proangiogenic, endothelial-protective, and calcium-modulating properties (44). Obese children are not only characterized by lower HDL cholesterol, as demonstrated in our study, but also HDL cholesterol function is disturbed (45).

STUDY LIMITATIONS. Although our 2D speckle tracking study comprises the largest number of children to date, we are aware of the limited sample size of Caucasian subjects, which confines our ability to draw general conclusions. In addition, although we had metabolic blood tests and lipid status in both obese and nonobese children and adolescents, data on the renin-angiotensin-aldosterone system, which may play a crucial role, were unfortunately not investigated.

It is important to note that although a significantly higher proportion of obese children had values above the 95th percentile for LV mass and LA diameter, and parameters for systolic and diastolic function were also significantly different between groups, this does not necessarily translate into clinically relevant functional impairment. Additionally, the cross-sectional study design does not provide information about potential reversibility of the changes with weight loss over time. Therefore, the clinical significance of these changed values in obese children remains unknown and will require extensive longitudinal follow-up to ultimately determine their predictive value.

CONCLUSIONS

The results of the present study demonstrate that childhood obesity is independently associated with significant changes in myocardial structure and function, indicating an early onset of potentially unfavorable alterations in the myocardium.

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KEY WORDS children, circumferential strain, echocardiography, longitudinal strain, obesity

APPENDIX For a supplemental table, please see the online version of this article.