Preclinical cardiovascular changes in children with obesity: A real-time 3-dimensional speckle tracking imaging study

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Abstract

The aims of this study were (1) to quantify changes in 3-dimensional (3D) strain in obese children using real-time 3D echocardiography (RT3DE) and 3D speckle tracking echocardiography (3DSTE), and (2) to investigate the utility of left ventricular (LV) strain variables in measuring early cardiovascular changes in children with obesity. A total of 181 obese children (study group) aged 4–18 years old were prospectively enrolled and compared with 229 healthy subjects (control group). We acquired demographic, clinical, biochemical, and 2D echocardiography/Doppler data. Also, RT3DE and 3DSTE were performed to measure LV volume, left ventricular ejection fraction (LVEF), LV mass (LVM), LV peak systolic global longitudinal strain (GLS), radial strain (GRS), circumferential strain (GCS), and global strain (GS). There were significant differences in anthropometric measurements, blood pressures, Cholesterol, C-reactive protein (CRP), Intima-media thickness (IMT), left atrium end-systolic dimension (LSDM), interventricular septal end-diastolic dimension (IVSD), LV posterior wall end-diastolic dimension (LVPWD), LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVEDD), LV end-diastolic volumes (LVEDV), and LV end-systolic volumes (LVESV), E and A velocities, E/A, e’, e’/a’, E/e’, LVM, LV mass index (LVMi), GLS, GRS, GCS, and GS between the study and control groups. The receiver operating characteristic curves (ROC) for the statistically significant echocardiographic variables showed that the range of areas of ROC curves varied from 0.76 (GLS), 0.74 (GRS), 0.72 (LASD), to 0.58 (LVESD), respectively. In conclusion, LV 3D strain variables by RT3DE and 3DSTE decrease in obese children. LV 3D strain is more sensitive than other echocardiographic and vascular ultrasound variables in detecting cardiovascular changes in children with obesity.
Competing interests: The authors have declared that no competing interests exist.

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; A, late transmural inflow velocities; a’, early diastolic mitral annular peak velocities; BMI, body mass index; BSA, body surface area; CAC, carotid artery compliance; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; E, early transmural inflow velocities; e’, early diastolic mitral annular peak velocities; EDV, end-diastolic volume; ESV, end-systolic volume; FMD, flow-mediated dilation; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; ICC, intra-class correlation coefficient; IMT, intima-media thickness; IVSD, interventricular septal end-diastolic dimension; LASD, left atrium end-systolic dimension; LDD-C, low-density lipoprotein cholesterol; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMi, left ventricular mass index; LVPWD, left ventricular posterior wall end-diastolic dimension; ROC, receiver operating characteristic; SBP, systolic blood pressure; STE, speckle tracking echocardiography; TDI, tissue doppler imaging; TG, triglycerides; WC, waist circumference.

Introduction

The prevalence of obesity has increased significantly in children and adolescents and has become a major risk factor for cardiovascular disease (CVD) [1–3]. It was reported that 60%-80% children with obesity would develop into adult obesity which is associated with left ventricle (LV) dilation, increased wall stress, hypertrophy, and heart failure [2,3]. In addition, obesity is associated with other risk factors, e.g., dyslipidemia, hypertension, glucose tolerance, inflammatory state, obstructive sleep apnea [4]. There is growing evidence that many of these cardiovascular changes occur in childhood and adolescence [5–9]. Identification of these risk factors is important because early prevention (primordial prevention) or treatment (primary prevention) to reverse the risk factors is most likely to be more effective [10].

Among the various co-morbidities, LV dysfunction remains the most significant cause of morbidity and mortality [2]. In addition to traditional LV functional measurements, e.g. LV ejection fraction, myocardial velocities determined by tissue doppler imaging (TDI) do not rely on geometric assumptions but are inherently unidimensional, angle-dependent, variable with age, and influenced by anthropometrics and heart rate [11,12]. Using both echocardiography and cardiac magnetic resonance imaging, myocardial strain has been shown to be more robust for assessment of regional ventricular myocardial function [13–17]. Currently, two-dimensional (2D) and three-dimensional (3D) speckle tracking echocardiography (STE) have been introduced to improve the accuracy of quantifying myocardial strain. Comparing with 2DSTE, 3DSTE has no geometrical assumption, unaffected by foreshortening of the LV, and more accurate and reproducible in patients with good image quality [18].

We have previously validated the feasibility, reproducibility and normal ranges of 3DSTE in children [19,20]. The aims of this study were (1) to quantify alterations in 3D strain in children with obesity using real-time 3D echocardiography and 3DSTE; and (2) to investigate the utility of LV strain variables in measurement of early cardiovascular changes in children with obesity.

Methods

Study population

The study was conducted prospectively in the 2nd Affiliated Hospital of Nanchang University in Nanchang, Jiangxi Province, China from March 2015 to October 2017. A total of 181 obese children and 229 healthy children who met the inclusion criteria were enrolled. Obese children were recruited from pediatric clinic and healthy children were recruited from department of physical examination.

Inclusion criteria: (1) Study group: children with BMI more than the 95th percentile for age and gender, respectively; (2) Control group: children with BMI less than the 85th percentile for age and gender, respectively (for both groups, the BMI reference values for the Chinese pediatric population [21] were used); (3) no CVD, determined by history, physical examination and conventional echocardiography; (4) consent was obtained.

Exclusion criteria: children with (1) secondary cause of obesity (such as known genetic syndromes); (2) structural heart disease; (3) other significant diseases, including hypertension, diabetes mellitus, thyroid disorder, renal disorder, autoimmune disease, and sleep apnea; (4) children taking any prescription medications; (5) poor echocardiographic windows and image quality, object with missing data.

The BMI of the children was calculated as BMI = body weight (kg)/height (m)^2.
The research protocol was approved by the Ethics Committee of the 2nd Affiliated Hospital of Nanchang University. Written informed consent was obtained from parents or guardians before enrollment.

**Clinical data**

Demographic and clinical data were obtained during the initial visit. Anthropometric measurements, including weight and height, were obtained and the BMI was calculated. Height was measured by wall-mounted stadiometers, weight by balance beam scales, waist circumference (WC) as the narrowest circumference between the margin of the lower rib and anterior superior iliac crest and hip circumference (HC) as the maximum circumference at the level of the buttock. Arterial blood pressure was measured using the right upper arm after a 10-minute rest in the supine position in a quiet room using calibrated cuff sphygmomanometers with appropriate cuff size [22]. Ultrasound measurements of subcutaneous fat thickness were taken at the posterior side of the upper arm above the triceps brachii.

**Laboratory blood biochemistry data**

Blood samples were collected from study subjects in the morning after an overnight fast and transferred to the laboratory immediately for analysis from March 2015 to October 2017. A fasting lipid panel was determined with the Friedewald equation. Fasting glucose levels were measured in a fluoride-oxalate sample. C-reactive protein (CRP) levels were measured with a high-sensitivity, double-antibody sandwich enzyme-linked immunosorbent assay. Plasma homocysteine levels were determined with a modified automated assay [23].

**Conventional echocardiographic assessment**

All conventional echocardiographic studies were performed using a Philips IE33 ultrasound system (Philips Medical System, Bothell, WA, USA) based on the guidelines of the American Society of Echocardiography [18]. All images were recorded and stored digitally for offline analysis. Measurements of the left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD) were acquired in the parasternal long-axis view obtained perpendicular to the LV long axis and measured at the level of the mitral valve leaflet tips, at the end of LV diastole and systole, respectively. Interventricular septal end-diastolic dimension (IVSD) and left ventricular posterior wall end-diastolic dimension (LVPWD) were measured in the basal ventricular segment of the respective myocardial wall at the end of diastole. Left atrium end-systolic dimension (LASD) was measured in the parasternal long-axis view perpendicular to the aortic root long axis, at the level of the aortic sinuses by using the leading-edge to leading-edge convention. In the apical 4-chamber view, early (E) and late (A) transmitral inflow velocities were determined using conventional pulsed-wave spectral Doppler echocardiography. Early (e’) and late (a’) diastolic mitral annular peak velocities were measured by pulsed-wave spectral TDI from the same view, on the septal side of the mitral annulus. All the measurements were repeated three times, and the average was calculated.

**Vascular measurements**

All the vascular measurements were performed with a 3–11 MHz linear-array transducer and the Philips IE33 system. Brachial artery flow-mediated dilation (FMD) was measured to assess endothelial function. The subjects were in the supine position. The dimension of the brachial artery was measured by calculating the distance between the proximal and distal intima (D1) during diastoles. Ischemia was caused for five minutes and the artery measurement was
repeated 60 seconds after ending the compression (D2) during diastoles. The FMD (%) was calculated through the equation: \( \text{FMD} = \frac{(D2-D1)}{D1} \times 100\% \) [24]. Measurements of carotid artery intima-media thickness (IMT), the end-systolic dimension (Ds) and the end-diastolic dimension (Dd) of the common carotid artery were taken on the far wall of the common carotid artery 10 mm proximal to the bifurcation [25]. The carotid artery compliance (CAC) was also calculated using the equation: \( \text{CAC} = \frac{(\text{Ds} - \text{Dd})}{\text{Dd}} \times \frac{\text{Ps} - \text{Pd}}{} \). \( \text{Ps} = \text{systolic blood pressure (SBP)}, \text{Pd} = \text{diastolic blood pressure (DBP)} \) [26].

**Real-time 3D and speckle tracking echocardiographic data**

A 1–3 MHz 3D matrix phased array transducer (X3-1) was used to acquire 3D data. A wide-angle acquisition “full volume” mode was used. The full-volume acquisition was recorded with four consecutive cardiac cycles from the LV apical four-chamber view during an end-expiration breath hold with a mean frame rate of \( \geq 20 \text{frames/sec} \). To optimize the acquisition frame rate \( \geq 20\text{Hz} \), the depth and the sector width were adjusted to ensure that the entire LV cavity was included within the pyramidal volume [19,20].

Offline analysis of the data was performed using Tom-Tec analysis software (Tom Tec Imaging System GmbH, Unterschleissheim, Bayern, Germany). For the tracing of the endocardium and epicardium, the following four views were displayed: (1) the apical four-chamber view; (2) the apical three-chamber view; (3) the apical two-chamber view; and (4) the apex of the LV. The LV epicardium and endocardium were traced automatically (Fig 1), and the tracings were refined manually. Afterwards, the software automatically performed calculation of LV end-systolic volume (ESV) and end-diastolic volume (EDV), left ventricular ejection fraction (LVEF), left ventricular mass (LVM), global longitudinal strain (GLS), global radial strain (GRS), global circumferential strain (GCS) and global strain (GS) by 3D-STE [19,20]. A final 16-segment Bullseye map and curves of strain values was displayed (Fig 2). The left ventricular mass index (LVMi) was calculated as LVM divided by body surface area (BSA). The BSA was calculated using the equation: \( \text{BSA} = 0.0061 \times \text{height (cm)} + 0.0128 \times \text{weight (kg)} - 0.1529 \).

In order to have access to information that could identify individual participants during or after data collection, all the children were numbered with their information being recorded in an excel form.

**Inter- and Intra-observer reproducibility**

The 3D data from 10 randomly selected subjects were analyzed twice at 1-week interval by one investigator for the intra-observer reproducibility. The interobserver reproducibility assessment was performed by analyzing data from 10 subjects who were chosen randomly by 2 independent investigators. The investigators were blinded to the other measurements.

**Statistical analysis**

All the analyses were performed using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA). The Shapiro-Wilk test was applied to ascertain normal distribution of parameters. Data from continuous variables were expressed as mean ± standard deviation. Differences in the normally distributed continuous data and categorical data were compared using the independent samples t-test and the chi-square test, respectively. The receiver operating characteristic (ROC) curve was also obtained to assess the sensitivity and specificity of the echocardiographic variables for assessing cardiovascular changes in the study group. Statistical tests were two-sided, and a \( P \) value < .05 was considered statistically significant. Inter- and intra-observer reproducibility values were evaluated using the intra-class correlation coefficient (ICC).
Results

The demographic and clinical data of the study group, i.e., children with obesity, and of the control group are shown in Table 1. There was no significant difference in gender, height between the two groups; however, the study group had significantly increased weight, BMI, WC, HC, SBP, DBP, heart rate, age and subcutaneous fat thickness ($P < 0.001$ to 0.05).

The blood chemistry data are shown in Table 2. There was no significant difference in fasting glucose, triglyceride, and homocysteine levels between the two groups; however, the study group had significantly higher low-density lipoprotein cholesterol (LDL-C), total cholesterol, high-density lipoprotein cholesterol (HDL-C), CRP levels ($P < 0.001$ to $< 0.05$) than those of the normal control group (Table 2).

The conventional echocardiographic data are summarized in Table 3. There was no significant difference in LVEF, $a'$ between the study group and control group. However, the study group had increased LASD, IVSD, LVPWD, LVEDD, LVESD, LVEDV, LVESV, LVM, LVMI, $E$, $A$, $e'$, E/A, E / $e'$ and $e'/a'$ ($P < 0.001$ to 0.05) than those of the control group.

Table 4 summarizes the vascular ultrasound data between the two groups. There was no significant difference in FMD and CAC between the study and the control groups. However, the study group had increased IMT than the control group ($P < 0.001$).

Table 5 shows the 3DSTE data for the 2 groups. Compared with the control group, the study group showed lower GLS, GCS, GRS and GS values ($P < 0.001$).

Moderate inverse correlations were found between the BMI and GLS ($r = 0.570$, $P < 0.05$), the BMI and GRS ($r = -0.521$, $P < 0.05$), the BMI and GCS ($r = 0.380$, $P < 0.05$), the LVM and
Fig 2. The 3-dimensional strain curves of the 16 segments of the LV in the controls (A) and in the obese subjects (B). The color-coded curves indicate the different myocardial segments of the left ventricle. The peak strain values of the several myocardial regions are decreased in the obese children compared with the controls.

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Table 1. Clinical data for obese and normal control groups.

|                | Control          | Obese            | P values |
|----------------|------------------|------------------|----------|
| Age (years)    | 11.49 ± 3.49     | 10.76 ± 2.72     | <.05     |
| Gender (male/female) | 113/116         | 104/77           | ns       |
| Height (m)     | 1.44 ± 0.20      | 1.47 ± 0.16      | ns       |
| Weight (kg)    | 37.87 ± 13.96    | 57.29 ± 19.25    | <.001    |
| BMI (kg/m²)    | 17.33 ± 2.58     | 25.67 ± 3.78     | <.001    |
| WC (cm)        | 63.77 ± 9.29     | 83.68 ± 11.66    | <.001    |
| HC (cm)        | 74.71 ± 13.02    | 88.90 ± 11.43    | <.001    |
| SBP (mm Hg)    | 101.41 ± 12.15   | 110.01 ± 12.91   | <.001    |
| DBP (mm Hg)    | 63.52 ± 9.58     | 69.71 ± 8.66     | <.001    |
| HR (bpm)       | 78.25 ± 10.87    | 81.83 ± 11.34    | <.005    |
| Subcutaneous fat (mm) | 4.70 ± 1.88 | 12.62 ± 4.01 | <.001 |

BMI, body mass index; WC, waist circumference; HC, hip circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

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GLS ($r = 0.411$, $P < 0.05$), the LVM and GRS ($r = -0.369$, $P < 0.05$), and the LVM and GCS ($r = 0.268$, $P < 0.05$).

In Table 6, the ROC for the statistically significant echocardiographic variables showed that the range of areas under the ROC curves varied from 0.76 (GLS), 0.74 (GRS), 0.72 (LASD), to 0.58 (LVESD) (Fig 3).

**Inter-observer and Intra-observer reproducibility**

Inter-observer agreement assessed by the ICC was 0.84, 0.83, 0.76 and 0.76 for GLS, GRS, GCS, and GS, respectively (Table 7), whereas intra-observer agreement ICC 0.78, 0.82, 0.79 and 0.87 for GLS, GRS, GCS, and GS (Table 8).

### Table 2. Laboratory biochemistry data comparing obese and normal control groups.

|                     | Control        | Obese          | $P$ values |
|---------------------|----------------|----------------|------------|
| Total cholesterol (mmol/l) | 4.01 ± 0.75    | 4.26 ± 0.88    | < .05      |
| LDL cholesterol (mmol/l)   | 2.16 ± 0.60    | 2.40 ± 0.65    | < .01      |
| HDL cholesterol (mmol/l)   | 1.37 ± 0.26    | 1.28 ± 0.29    | < .01      |
| TG (mmol/l)            | 1.46 ± 1.15    | 1.35 ± 0.91    | ns         |
| Fasting glucose (mmol/l) | 5.05 ± 0.68    | 5.00 ± 0.53    | ns         |
| CRP (mg/l)             | 3.13 ± 1.43    | 3.13 ± 3.07    | < .001     |
| Homocysteine (μmol/l)   | 10.05 ±6.65    | 10.26 ± 8.57   | ns         |

TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein.

### Table 3. Conventional echocardiographic data comparing obese and normal control groups.

|                     | Control        | Obese          | $P$ values |
|---------------------|----------------|----------------|------------|
| LASD (mm)           | 25.11 ± 3.73   | 28.57 ± 4.32   | < .001     |
| IVSD (mm)           | 6.20 ± 1.36    | 7.22 ± 1.48    | < .001     |
| LVPWD (mm)          | 6.35 ± 1.33    | 7.11 ± 1.39    | < .001     |
| LVEDD (mm)          | 39.29 ± 4.95   | 41.74 ± 4.52   | < .001     |
| LVESD (mm)          | 24.57 ± 3.81   | 26.32 ± 3.55   | < .001     |
| LVEDV (ml)          | 68.77 ± 20.55  | 76.74 ± 22.23  | .001       |
| LVESV (ml)          | 22.91 ± 10.30  | 27.47 ± 10.46  | < .001     |
| LVEF (%)            | 67.84 ± 5.80   | 66.11 ± 5.38   | ns         |
| E (cm/s)            | 108.56 ± 13.63 | 112.83 ± 14.91 | < .05      |
| A (cm/s)            | 57.19 ± 10.60  | 63.90 ± 12.67  | < .001     |
| E/A                 | 1.95 ± 0.36    | 1.82 ± 0.40    | < .01      |
| E' (cm/s)           | 12.88 ± 1.41   | 11.99 ± 1.84   | < .001     |
| a' (cm/s)           | 6.93 ±6.27     | 7.13± 1.73     | ns         |
| E'/a'               | 2.10 ± 0.49    | 1.75 ± 0.38    | < .001     |
| LVM (g)             | 71.08 ± 29.84  | 99.32 ±43.05   | < .001     |
| LVM (g/m²)          | 57.20 ± 14.21  | 66.15± 20.59   | .001       |

LASD, left atrium end-systolic dimension; IVSD, interventricular septal end-diastolic dimension; LVPWD, left ventricular posterior wall end-diastolic dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; E, mitral E wave peak velocity; A, mitral A wave peak velocity; e', peak e-wave velocity by tissue Doppler imaging; a', peak a-wave velocity by tissue Doppler imaging; LVM, left ventricular mass; LVMII, left ventricular mass index.
Discussion

We evaluated the association between obesity and cardiovascular changes using clinical, biochemical, vascular ultrasound, and echocardiographic (2D, Doppler, and RT3DE/3DSTE) variables. In addition to an increase in weight, adiposity variables, our study showed significant differences in blood pressures, cholesterol levels, IMT, LV size, wall thickness, mass, and systolic and diastolic function in children with obesity. In this cohort, there was no difference in vascular ultrasound variables (FMD and CAC). In contrast, the 3D strain variables were significantly diminished in obese children compared with those in the normal control group. Finally, the ROC analysis showed that 3D LV strain variables, LASD are the most sensitive variables to detect LV changes associated with obesity in children.

Based on the strengths and limitations of the conventional echocardiographic measurement of LV function [27], we previously validated the feasibility, reproducibility, maturational changes, and normal ranges of 3D strain and other variables of the LV in normal children using RT3DE and 3DSTI technologies [19,20]. In this study, we applied these LV 3D strain analyses to evaluate children with obesity.

There are a few findings in this study worthy of discussion. First, the age of our study group was 11.5 ± 3.5 years, representing early cardiovascular changes associated with obesity. Obesity can lead to cardiac output increase and high LV wall tension, which may result in thickening of LV wall to compensate LV wall tension [28]. On the other hand, LV hypertrophy adapts to the enlargement of LV cavities and impairment of diastolic function while global systolic function is preserved. Previous epidemiological studies [4–6,8–10] have shown that obesity is associated with cardiovascular alterations, including atherosclerotic changes in autopsies, subclinical structural and functional alterations by vascular ultrasound studies, and other risk factors for CVD such as hypertension, dyslipidemia, insulin resistance, and metabolic syndrome in children and adolescents. On the other hand, obesity, with or without hypertension, can also cause left ventricular remodeling, e.g. increased left ventricular chamber dimensions, volumes, wall thickness, and mass. Our study results suggested that LV adaptation and remodeling may occur at a young age in obese children and precede other cardiovascular changes that have been shown in adolescents and young adults with obesity or other CVD risk factors.

Table 4. Vascular ultrasound data comparing obese and normal control groups.

|                  | Control        | Obese          | P values |
|------------------|----------------|----------------|----------|
| FMD (%)          | 10.18 ± 2.00   | 10.44 ± 1.82   | ns       |
| IMT (mm)         | 0.36 ± 0.08    | 0.46 ± 0.10    | <.001    |
| CAC (%/mm Hg)    | 0.15 ± 0.08    | 0.15 ± 0.06    | ns       |

FMD, flow-mediated dilation; IMT, intima-media thickness; CAC, carotid artery compliance.

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Table 5. Three-dimensional speckle tracking echocardiography global parameters comparing obese and normal control groups.

|                  | Control        | Obese          | P values |
|------------------|----------------|----------------|----------|
| GLS (%)          | -21.12 ± 2.99  | -17.57 ± 3.13  | <.001    |
| GRS (%)          | 41.56 ± 5.19   | 35.37 ± 5.58   | <.001    |
| GCS (%)          | -28.36 ± 4.21  | -24.34 ± 4.99  | <.001    |
| GS (%)           | -33.48 ± 4.01  | -30.10 ± 5.03  | <.001    |

GLS, global longitudinal strain; GRS, global radial strain; GCS, global circumferential strain; GS, global strain.

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Secondly, we demonstrated that the LV 3D strain variables decreased in obese children and that these variables are sensitive for detecting myocardial functional alterations. The reasons for these findings are likely related to adiposity and myocardial abnormality in obesity. Fat accumulation causes irregular adipose tissue aggregation between the myocardial cells, pressure increase, myocardial cell atrophy, and cardiac dysfunction [29]. Furthermore, the hormones and proinflammatory cytokines that the adipose cells secrete may affect myocardial remodeling [30], i.e. LV enlargement, hypertrophy, diastolic dysfunction, and 3D strain abnormalities but preserved LVEF [31–35]. Although our obese subjects had a normal LVEF, they demonstrated evidence of impaired systolic function manifested by decreased LV systolic strain. The abnormalities in cardiac function observed in our subjects likely involve myocardial fibers which affect myocardial deformation. These results suggest that conventional measures of cardiac function, e.g. LVEF, may not provide sensitive assessment of early alteration of cardiac dysfunction, while 3D-STE has the capabilities.

Thirdly, our data showed that GLS, GRS, GCS, and GS were significantly decreased in obese children without comorbidities. These findings are consistent with results from previous studies that showed similar differences using different methods and measurements for LV strain variables [5,8,36], whereas they differ from others that showed there was no difference in LV strain variables in obese children [6,37]. The heterogeneity in the results from the previous studies can be explained as follows: (1) STE is based on tracking and measurement of tissue displacement. Whereas 2DSTE tracks speckle movement on 2D planes, cardiac movement is 3D. As a result, 2DSTE tracks the projections of the speckles moving out of the plane, which are less than the real distance between the speckles. In contrast, 3DSTE is free of geometric assumptions and speckles moving out of the scanning plane. Therefore, 3DSTE is likely more accurate than 2DSTE for evaluating LV strain variables. (2) LV strain results calculated using different echocardiographic systems, software, and algorithms can also cause variabilities in strain measurements, as with previous studies using different echocardiographic systems and tracking algorithms [38]. (3) Age, gender, and ethnicity may also contribute to the variable LV strain results in obese children in the literature.

### Table 6. Area under ROC curve for the echocardiographic variables.

| Test Result Variable(s) | Area | Asymptotic 95% Confidence Interval |
|-------------------------|------|----------------------------------|
| GLS                    | 0.76 | 0.69                             |
|                         |      | 0.84                             |
| GRS                    | 0.74 | 0.65                             |
|                         |      | 0.83                             |
| GCS                    | 0.71 | 0.60                             |
|                         |      | 0.81                             |
| LVM                    | 0.71 | 0.62                             |
|                         |      | 0.79                             |
| IVSD                   | 0.72 | 0.64                             |
|                         |      | 0.81                             |
| LASD                   | 0.72 | 0.63                             |
|                         |      | 0.81                             |
| LVEDD                  | 0.62 | 0.53                             |
|                         |      | 0.71                             |
| LVMI                   | 0.63 | 0.52                             |
|                         |      | 0.74                             |
| LVPWD                  | 0.73 | 0.66                             |
|                         |      | 0.81                             |
| LVESD                  | 0.58 | 0.48                             |
|                         |      | 0.67                             |

GLS, global longitudinal strain; GRS, global radial strain; GCS, global strain circumferential; LVM, left ventricular mass; IVSD, interventricular septal end-diastolic dimension; LASD, left atrium end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVMI, left ventricular mass index; LVPWD, left ventricular posterior wall end-diastolic dimension; LVESD, left ventricular end-systolic dimension; IMT, intima-media thickness; FMD, flow-mediated dilatation; LVEF, left ventricular ejection fraction; CAC, carotid artery compliance

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Finally, among the CVD risk factors, BMI is found to be an independent predictor of worsening LV systolic and diastolic function [32]. Our study showed that 3D LV strain variables appeared to be more closely related to BMI than to LVM as was reported in the previous
studies, e.g. BMI is more closely associated with a decrease in GLS [37,39], GCS, or GRS in our study. Left ventricular hypertrophy induced by increased wall stress can damage the subendocardial myocardial fibers, which are responsible for regional myocardial function [40]. In our study, cholesterol levels were significantly higher in the obese group than in the control group, which are similar to the findings from a previous study [41–43], whereas there was no difference in TG, fasting glucose, and homocysteine levels between the obese and the control group. In our study, IMT was significantly higher in the obese group than in the control group, which are similar to the findings from a previous study [42], however there was no significant difference in FMD, and CAC among obese and control subjects, unlike some of the previous studies [26,44]. Again, the differences may be explained by the younger age, the ethnicity of the subjects, and other variables in this study.

Limitations
There are limitations in this study. First, all subjects were Chinese in ethnicity. The data and results may be different for other ethnic groups. There were incomplete data in demographic, echocardiography and blood chemistry, due to the concern of the subject and their families. Further research is necessary to assess the variability of 3D STE for the evaluation of LV 3D strain in other ethnic population. Second, strain measurements among different vendors had inter-vendor variability. The use of a single vendor is appropriate for early research applications, but clinical applications in large populations across multiple imaging platforms need standardization. Finally, 3D STE is highly dependent on image quality, especially endocardial boundary delineation, and its low frame rate may lead to miscorrelation among frames and affect strain data accuracy. Technology will likely improve in temporal resolution, sector size and width, and more modality independent and automated 3D speckle tracking echocardiographic computational algorithms.

Conclusions
LV 3D strain variables by 3DSTE are decreased in young obese children. LV 3D strain variables are more sensitive than other conventional echocardiographic and vascular ultrasound variables in detecting early cardiovascular abnormalities in children with obesity.

Table 7. Inter-observer variability of GLS, GCS, GRS, and GS by 3D-STE.

|                | Observer1   | Observer2   | ICC   |
|----------------|-------------|-------------|-------|
| GLS (%)        | -18.46±2.95 | -18.68±2.93 | 0.83  |
| GRS (%)        | 38.75±7.01  | 37.01±6.02  | 0.84  |
| GCS (%)        | -27.45±5.43 | -25.37±4.96 | 0.76  |
| GS (%)         | -33.08±5.55 | -31.40±4.13 | 0.76  |

ICC, intraclass correlation coefficient.

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Table 8. Intra-observer variability of GLS, GCS, GRS, and GS by 3D-STE.

|                | Observer1   | Observer2   | ICC   |
|----------------|-------------|-------------|-------|
| GLS (%)        | -19.63±3.83 | -19.52±3.30 | 0.78  |
| GRS (%)        | 41.64±6.17  | 42.17±4.91  | 0.82  |
| GCS (%)        | -30.42±3.92 | -31.09±3.29 | 0.79  |
| GS (%)         | -34.84±3.25 | -35.63±3.44 | 0.87  |

ICC, intraclass correlation coefficient.

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Supporting information

S1 Table. Control and obese group data.
(XLS)

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