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Markers of Cardiovascular Risk, Insulin Resistance, and Ventricular Dysfunction and Remodeling in Obese Adolescents

Aura A. Sanchez, M.D.[1], **Philip T. Levy, M.D.**[1], **Timothy J. Sekarski, R.D.C.S.**[1], **Ana M Arbelaez, M.D.**[1], **Charles F Hildebolt, D.D.S., Ph.D.**[2], **Mark R. Holland, Ph.D.**[3], and **Gautam K. Singh, M.D.**[1]

[1] Department of Pediatrics. Washington University School of Medicine, Saint Louis, MO

[2] Mallinkrodt Institute of Radiology. Washington University School of Medicine. Saint Louis, MO.

[3] Department of Radiology & Imaging Sciences. Indiana University School of Medicine. Indianapolis, IN.

Abstract

Objectives—To test our hypothesis that obese adolescents have left ventricular (LV) dysfunction and remodeling that are associated with markers of cardiovascular risk and insulin resistance (IR).

Study design—In a cross-sectional study of 44 obese and 14 lean age-, sex-, Tanner stage-, and race-matched adolescents, IR, markers of cardiovascular risks, conventional and 2-dimensional speckle tracking echocardiography (2DSTE) measures of LV function and structure were evaluated and compared.

Results—The obese adolescents had significantly increased body mass index (BMI) Z-score, systolic blood pressure, fasting insulin, IR, and atherogenic lipids compared with the lean adolescents. A subgroup of obese adolescents had LV remodeling characterized by significantly increased LV mass index (LVMI, $g/m^{2.7}$) and relative wall thickness (RWT). Almost all obese adolescents had LV dysfunction with peak LV global longitudinal strain (GLS,%), systolic global GLS rate (GLSR, %/s) and early diastolic GLSR significantly lower than in lean adolescents and in the normal pediatric population. BMI Z-score predicted LV remodeling [LVMI (R^2= 0.34) and RWT (R^2 0.10], and peak LV GLS (R^2 0.15), and along with systolic blood pressure, predicted systolic GLSR (R^2 0.16); ($P \leq 0.01$ for all). Fasting insulin predicted early diastolic GLSR (R^2 0.17, $P \leq 0.01$).

Address for correspondence: Gautam K. Singh, M.D. One Children's place Campus Box 8116-NWT St. Louis, MO 63110 Phone: 314-454-6095 Fax: 314-454-2561 singh_g@kids.wustl.edu.

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Conclusions—Obese adolescents have subclinical ventricular dysfunction associated with the severity of obesity, increased systolic blood pressure, and IR. Ventricular remodeling is present in a subgroup of obese adolescents in association with the severity of obesity. These findings suggest that obesity may have an early impact on the cardiovascular health of obese adolescents.

Keywords

cardiac function; structure; obesity; adolescence

Emerging evidence suggests that although obese adults have increased conventional cardiovascular risk factors, hemodynamic load, and neuro-hormonal activation, but those contributing factors cannot entirely explain the reported changes in ventricular structure and function that lead to heart failure[6,7]. There are intrinsic alterations in the myocardium that are independent of load. Insulin resistance (IR) promotes alterations in myocardial substrate metabolism, evident by increases in myocardial fatty acid uptake, utilization and oxidation that may play a role in the pathogenesis of decreased myocardial efficiency and cardiac dysfunction in obese individuals[8]. Studies in obese children and adolescents have shown ventricular remodeling and subclinical impairment in diastolic function but have not discerned the association between ventricular dysfunction and markers of cardiovascular risks or IR in this population[9-11].

We measured clinical and metabolic markers of cardiovascular risk and IR, and assessed the left ventricular (LV) structure and function in lean and obese adolescents Our hypothesis was that obese adolescents have subclinical LV dysfunction and remodeling associated with markers of modifiable cardiovascular risk and IR.

Methods

Using a cross-sectional study approach we studied a group of obese adolescents (body mass index, BMI ≥95th percentile for age and sex)[14] referred to the Washington University Outpatient Pediatric Preventive Cardiology Clinic at St. Louis Children's Hospital from January 2007 to December 2012. Subjects were eligible for inclusion if they were 12 to 18 years of age, Tanner stage III or higher, and had complete echocardiographic and laboratory evaluations performed during the study period. Subjects were excluded if they had heart disease, diabetes, or other endocrinopathies, pregnancy, or a history of substance and alcohol abuse, smoking, obstructive sleep apnea, use of pharmaceutical agents that affect IR or had a poor acoustic windows for echocardiographic evaluation. A cohort of healthy, lean (BMI < 85th and > 5th percentile for age and sex), age, sex, race, and Tanner stage matched (for minimizing the potential confounding effects on IR)[2] subjects from a simultaneous study in our institution was used as a control group[15]. In addition, data from normal healthy, lean, age- (12 to 18 years) and sex-matched pediatric cohort (n = 51) from our echocardiography laboratory were included to provide the range of normal pediatric values of echocardiographic functional [16,17]. The Institutional Review Board for human studies at Washington University approved the study. Written informed consent was obtained from the parents/guardians of the study subjects.

All subjects underwent a comprehensive clinical evaluation as part of the standard of care. Demographic and anthropometric variables were collected. BMI (kg/m^2) was transformed into BMI Z-score to adjust for age and sex. Three measurements of systemic blood pressure (mmHg) were taken using a manual sphygmomanometer with the appropriate cuff size in resting position. Hypertension was defined based on the average systolic or diastolic blood pressure percentiles for age, sex, and height: pre-hypertension (≥ 90^{th} but < 95^{th}), stage I (≥ 95^{th} but < 99^{th}, plus 5 mmHg) and stage II (>99^{th}, plus 5 mmHg)[19]. The metabolic assessment was performed after a 12-hour overnight fasting and included plasma glucose (mg/dl), plasma insulin (μU/mL), and lipids (total cholesterol, triglycerides, high-density lipoprotein - HDL cholesterol, low-density lipoprotein - LDL cholesterol, mg/dl). Dyslipidemia and hyperglycemia were defined according the published criteria for the pediatric population[20, 21]. Variables used to define metabolic syndrome were considered as markers of cardiovascular risk and included BMI Z-score, systemic blood pressure, fasting glucose and lipid profiles[22]. For IR indices, we used the reciprocals of homeostasis model assessment of insulin sensitivity [HOMA-IS = 22.4/ Glucose (mg/dL) x Insulin (μU/mL)] and the fasting plasma insulin (mL/μU).

Assessment of cardiac structure and function

Left ventricular structure—A transthoracic complete M-mode, 2-dimensional (2D) and Doppler echocardiographic examination was performed with a commercially available ultrasound imaging system using a phased array transducer of appropriate frequency (Vivid 7 and 9; General Electric Medical Systems, Milwaukee, WI, USA). Using M-mode imaging of the LV in the parasternal short-axis view, relative wall thickness (RWT) and LV mass (Devereux formula) were calculated and LV mass was indexed to $height^{2.7}$ (LVMI, $g/m^{2.7}$)[24, 25]. The 95th percentiles for LVMI for children older than 9 years of age (> 40 $g/height^{2.7}$ in females and >45 $g/height^{2.7}$ in males) and the 95^{th} percentile value for RWT for normal children and adolescents (RWT > 0.41) were used as cut-off values to categorize LV structure (geometry)[26, 27].

Left ventricular function—LV fractional shortening (FS) and biplane LV ejection fraction (EF) were measured according to the guideline of the American Society of Echocardiography[24]. Myocardial mechanics were analyzed by the quantification of LV longitudinal strain and strain rate. Strain (%) describes the fractional changes in the dimension of a myocardial fiber/segment. Myocardial strain rate (%/s) is the rate of change in strain and represents fiber contractility[13]. LV global longitudinal strain (GLS, %) and systolic and diastolic global longitudinal strain rates (GLSR, %/s) were measured by using validated 2DSTE [28]. A single observer, who was blinded to the subjects' clinical and metabolic values analyzed peak LV GLS, systolic GLSR, and early and late diastolic GLSR values using vendor software (EchoPAC,TM General Electric Medical Systems, Waukesha, WI, USA). Our echocardiography laboratory has previously demonstrated high reproducibility of strain measurements[28]. We further tested the reproducibility of GLS and GLSR in 7 age- (12 – 18 years), sex- (4 male) and BMI z score- (1.82 – 2.32) matched obese adolescents at two time points at 6 weeks interval.

Statistical analyses

Continuous data were tested for normality with the Shapiro-Wilk W test and equality of variances was tested with the O'Brien, Brown-Forsythe, Levene, Bartlett, and F Tests. The t test and the Wilcoxon rank sums test were used for data with normal and non-normal distribution and/or variances respectively. Because structure and function in the heart are closely linked[29] the adolescent cohort was further divided into obese with normal LV structure (normal LVMI and RWT, "Normal Obese") and obese with abnormal LV structure (abnormal LVMI and RWT, "Abnormal Obese"). Comparisons were made among the "abnormal" and "normal" obese adolescents and lean control groups by using oneway ANOVA, with two planned contrasts for the comparisons of interest: obesity (lean vs. all obese adolescents) and abnormal LV structure ("Normal Obese" vs. "Abnormal Obese" adolescents). Bivariate analyses and backward stepwise multiple linear regression analyses were used to determine which variables best predicted changes in LV structure and function for the entire cohort of lean and obese subjects as well as for the cohort of obese subjects only. To predict LV structure and function, BMI Z-score, systolic blood pressure, and fasting insulin were used as independent variables[27, 30, 31]. The maximum R^2 from K-fold cross validation was used for the multiple linear regression analyses. A p value ≤ 0.05 was considered statistically significant. Using data on differences in fasting insulin levels between obese and lean children from a previous study[15] and with alpha set at 0.05, a two-tailed test determined a sample size of 13 in each group and a power of 80.1%. We enrolled more than 13 obese adolescents in the study group at the outset. Statistical analyses were performed with JMP Statistical Software 10.0.0 (SAS Institute, Inc., Cary, NC), StatXact 10 (Cytel, Inc., Cambridge, MA), and Power and Precision 4.0 (Biostat, Inc., Englewood, NJ).

Results

A total of 44 out of 57 obese adolescents were included in this study. Thirteen subjects were excluded due to incomplete laboratory data and inadequate acoustic windows. Fourteen lean adolescents from a simultaneous study in our institution were used as a control group[15]. Tables I and II display the demographic, clinical and metabolic characteristics of the study population. Obese adolescents had significantly increased HOMA-IR, fasting insulin levels, systolic blood pressure and lipid measurements. Pre-hypertension and stage I hypertension were found in 9 (20%) and 4 (9%) obese adolescents, respectively. None had stage II hypertension. Thirty-seven (84%) obese adolescents had dyslipidemia but none had hyperglycemia. All lean subjects had normal blood pressure, fasting glucose and lipids.

Assessment of cardiac structure and function

Left ventricular structure—The results of analyses of the measurements of LV structure are shown in Table III. Ten ("Abnormal Obese") of the 44 obese adolescents (23%) had abnormal LV geometry based on their LVMI and RWT measurements; 4 had concentric remodeling, 1 had concentric hypertrophy and 5 had eccentric hypertrophy. There was no difference in age between the obese subjects with normal and abnormal cardiac geometry (14.4 ± 1.8 vs. 14.5 ± 2.4, p=0.86). All the lean adolescents had normal LV geometry. There was no significant correlation with fasting glucose and lipid variables. Backward stepwise multiple linear regression analyses retained only BMI Z score as a predictor for LVMI ($P <$

0.01, $R^2 = 0.34$) as well as for RWT ($P = 0.01$, $R^2 = 0.10$). The association was positive, and residuals were normally distributed (Shapiro-Wilk W test, $P = 0.43$ and 0.41respectively).

Left ventricular function—The LV GLS was significantly lower in obese compared with lean subjects and significantly lower in “abnormal obese” than in “normal obese” (Figure and Table III), indicating greater systolic dysfunction in the “abnormal obese” group. The LV early diastolic GLSR was significantly lower in obese than in lean subjects and significantly lower in “Abnormal Obese” than in “Normal Obese” (Figure and Table III), indicating greater diastolic dysfunction in the “Abnormal Obese” group. In obese cohort, only 5 (11%) subjects had GLS values (mean -18.7 %; 25th – 75th percentile -16.9 % to -19.2 %) and early diastolic GLSR (mean 1.4 1/s; 25th – 75th percentile 1.3 to 1.5 1/s) values > 25th percentile of the control subjects (-16.5 % and 1.2 1/s respectively) and normal pediatric values (-19.5 % and 1.55 1/s respectively). The mean values of GLS and early diastolic GLSR for the entire cohort were less than the 5^{th} percentile of the normal pediatric values. Thus, although LV FS and EF were normal, almost all obese adolescents had subclinical systolic and early diastolic dysfunction.

Backward stepwise multiple linear regression analyses for the entire cohort of lean and obese subjects retained BMI Z-score as the only predictor for peak GLS ($P \leq 0.01$, $R^2 = 0.15$). The residuals were normally distributed (Shapiro-Wilk W test, $P = 0.39$). BMI Z-score and systolic blood pressure were found to be predictors for systolic GLSR. The model was significant ($P \leq 0.01$, $R^2 = 0.16$) and the residuals were normally distributed. Fasting insulin was the only predictor for early diastolic GLSR ($P = 0.03$, $R^2 = 0.22$). The residuals were again normally distributed (Shapiro-Wilk W test, $P = 0.62$). When the data were analyzed by backward stepwise multiple linear regression for the obese subjects only, BMI Z-score was retained as the only predictor for peak GLS ($P = 0.05$, $R^2 = 0.12$), systolic blood pressure for systolic GLSR ($P = 0.03$, $R^2 = 0.15$), and fasting insulin for early diastolic GLSR ($P = 0.01$, $R^2 = 0.17$). The residuals were again normally distributed for all.

Reproducibility—The intra-observer and inter-observer reproducibility for LV GLS had a bias of 7% with LOA -3.7 to 3.3 and 8% with LOA -4.5 to 3.5 respectively by Bland Altman analysis, coefficient of variation 6 and 7 respectively, and linear correlation of 0.84 and 0.78 (p-value <0.001 for both) respectively. The intra-observer and inter-observer reproducibility for LV early diastolic GLSR had a bias of 16% with LOA -1.1 to 1.1 and 17% with LOA -1.2 to 1.2 respectively, coefficient of variation 13 and 17 respectively, and linear correlation of 0.81 and 0.70 (p-value <0.001 for both) respectively. Both intra- and inter-observer reproducibility for late diastolic GLSR were poor with wider LOA (-2.1 to 2.5), higher coefficient of variation (>25) and modest linear correlation (<0.35). Thus, the reproducibility in obese adolescents was the most robust for GLS, good for early diastolic GLSR but poor for late diastolic GLSR.

Discussion

A subgroup of obese adolescents (“Abnormal Obese”) had LV remodeling characterized by significantly increased LVMI and RWT that were exclusively and positively correlated with BMI Z-score. This was in agreement with similar findings in previous studies in obese

adolescents that suggested that the severity of obesity may directly affect LVM and ventricular remodeling[33]. None of the metabolic and cardiovascular risk factors were predictive of ventricular remodeling as they were not significantly different between "Abnormal Obese" and "Normal Obese". It is possible that the duration of obesity may play an important role in the development of ventricular remodeling[34]. Those who have longer duration of obesity appears to develop more severe alterations in LV geometry[34]. This could explain the presence of LV remodeling in only ten (23%) of the obese adolescents in our study. Potential mechanisms involved in LV remodeling could be increased neuro-hormonal activity due to excessive visceral adipose tissue and overall increased lean mass, predisposing obese individuals to a high preload and afterload state[6, 34]. Studies in children and adolescents also have shown that IR has an incremental effect on LV mass in those with a greater degree of adiposity[30].

Our study demonstrates that the majority of obese adolescents had subclinical systolic and early diastolic dysfunction, even when conventional echocardiographic measurements showed normal values. The magnitude of the decrement in LV GLS and early diastolic GLSR was greater in obese adolescents with abnormal LV structure than in those with normal LV structure. The LV GLS and early diastolic GLSR in 90% of obese adolescent were significantly lower than those in the lean control group, were well below the 5th percentile of the normal pediatric values[17]; and were present even in those with less severe obesity and normal LV structure ("Normal Obese"). These results confirm previous reports that obese adolescents and adults, with normal function by conventional measures have decreased GLS and early diastolic GLSR in association with the severity of obesity.[7, 31] These results raise the question of whether ventricular dysfunction may precede the development of ventricular structural abnormalities in some of obese adolescents. The development of ventricular dysfunction may serve as an early marker of cardiovascular involvement before the manifestation of cardiac clinical and structural signs of the impact of obesity.

Decreased diastolic GLSR in obese adolescents in our study was predicted by IR, which is consistent with a previous study that showed that the peak LV systolic strain rate correlated with HOMA-IR and insulin levels, but not with BMI, duration of obesity, and LVMI[14]. Another study assessed cardiac function in obese children using 2DSTE and showed that LV GLS negatively correlated with HOMA-IR and BMI Z-score[35]. However, the multivariate analysis performed in this study did not include measures of IR. Our results show that IR may be a predictor of decreased diastolic GLSR, independently of BMI, lipids, and systolic blood pressure.

This study had several limitations, including small sample size. The absence of direct measurement of lipoprotein subclasses by nuclear magnetic resonance spectroscopy[39] may have led to underestimation of lipoproteins and the possible association with LV mechanics. There is evidence that obese adolescents have compensatory increase in LV radial deformation and torsion measured with three-dimensional wall motion tracking imaging[40]. However, reliable radial and circumferential deformation measurement is often difficult due to an inadequate view and suboptimal myocardium tracking in the parasternal short-axis view, we only evaluated LV longitudinal myocardial deformation, which is the most reliably

measured component of LV mechanics[13, 28]. The correlations of LV functional measures with BMI, systolic blood pressure and IR were modest. The findings in this study suggest that obesity may have an early impact on cardiac function in obese adolescents. This finding deserves further study in larger populations.

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Abbreviations

IR	Insulin resistance
LV	Left ventricular
2DSTE	2-dimensional speckle tracking echocardiography
BMI	Body mass index
HOMA-IR	Homeostasis model assessment of insulin resistance
LVMI	Left ventricular mass index
RWT	Relative wall thickness
GLS	Global longitudinal strain
GLSR	Global longitudinal strain rate
MetS	Metabolic syndrome
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
FS	Fractional shortening
EF	Ejection fraction

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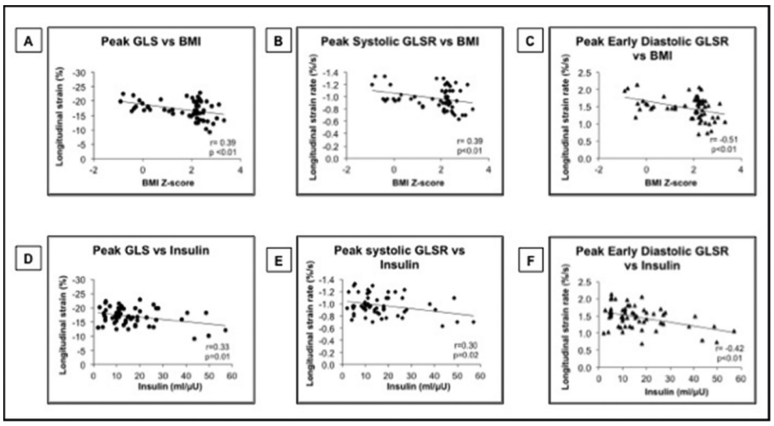

Figure.

Relationship between BM Z-score and fasting insulin with LV longitudinal deformation variables. (A) Correlation between LV peak GLS and BMI Z-score. (B) Correlation between LV peak systolic GLSR and BMI Zscore. (C) Correlation between LV peak early diastolic GLSR and BMI Z-score. (D) Correlation between LV peak GLS and fasting insulin. (E) Correlation between LV peak systolic GLSR and fasting insulin. (F) Correlation between LV peak early diastolic GLSR and fasting insulin.

Table 1

Subject demographics by LV structure

	Control subjects	Obese subjects		P value	P value
	Lean (n=14)	**Normal (n=34)**	**Abnormal (n=10)**	**Control subjects vs. Obese subjects**	**Obese subjects Normal vs. Abnormal**
Age, years	15 (13–17)	14 (13–16)	14 (12–15)	0.11	0.94
*Gender (M/F)	8/6	21/13	7/3	0.76	0.91
†Tanner stage	1/9/04	5/13/16	1/4/5	0.12	0.86
‡Race	12/2/0/0	20/7/7/0	5/2/0/3	0.19	0.32
BMI, kg/m^2	20 (17–23)	32 (30–38)	41 (30–53)	<0.001	0.52

Values are median (25th– 75th percentile).

Normal, Normal LV structure; Abnormal, Abnormal LV structure

For gender, Tanner stage and race, values are the number of subjects.

*Gender: Male/ Female.

†Tanner stage: III/IV/V.

‡Race: White/ Black/ Asian/ Unknown.

Table 2

Insulin resistance indices and markers of cardiovascular risk in obese adolescents with normal and abnormal LV structure

	Control subjects	Obese subjects		P value	P value
	Lean (n=14)	Normal (n=34)	Abnormal (n=10)	Control subjects vs. Obese subjects	Obese subjects Normal vs. Abnormal
Insulin resistance indices					
Fasting Insulin, mL/uU	8.3 (2.70–14.80)	15.65 (5.00–26.00)	16.50 (3.50–24.00)	0.004	0.79
HOMA-IR, Umol	1.8 (0.57–2.66)	3.45 (1.01–5.13)	3.46 (0.67–5.08)	0.007	0.66
Markers of cardiovascular risk					
BMI Z-score	−0.115(−0.46-0.145)	2.24 (1.78–2.38)	2.35 (1.61–2.65)	<0.001	0.28
Systolic blood pressure (mm/Hg)	109.00 (98.00-120.00)	115.50 (100.00–122.00)	109.50 (101.00–116.50)	0.03	0.35
Diastolic blood pressure (mm/Hg)	68 (57.00 -76.00)	66.00 (60.00–72.00)	69.00 (55.50–77.00)	0.49	0.59
Fasting glucose, mg/dL	88.80 (81.00–98.00)	86.00 (77.90–90.00)	82.50 (75.50–80.00)	0.34	0.49
Total cholesterol, mg/dL	126.70 (92–176.00)	212.00 (146.20–238.00)	185.50 (157.00–208.00)	<0.001	0.46
Triglycerides, mg/dL	64 (30.00–160.00)	170.50 (90.80–236.00)	131.50 (77.00–281.00)	<0.001	0.78
LDL cholesterol, mg/dL	69 (53.00 - 110.00)	126.00 (67.00–155.50)	120.00(59.50 - 133.00)	<0.001	0.21
HDL cholesterol, mg/dL	44.70 (31.00–60.00)	42.00 (26.90–48.00)	36.50 (33.00–39.00)	0.39	0.41

Values are median (25 th– 75 th percentile).

Normal, Normal LV structure; Abnormal, Abnormal LV structure

Table 3

Echocardiographic assessment of left ventricular structure and function in obese adolescents with normal and abnormal LV structure.

	Control subjects	Obese subjects		P value	P value	Normal Pediatric
	Lean (n=14)	Normal (n=34)	Abnormal (n=10)	Control subjects vs. Obese subjects	Obese subjects Normal vs. Abnormal	Values (n=51)
Left ventricular structure						
LVMI, g/height2.7	23.6 (18.85-29.34)	33.50 (23.00–36.89)	44.24 (19.94–45.33)	<0.001	<0.001	26.25 (22.87–27.45)
RWT	0.3 (0.17-0.49)	0.30 (0.22–0.34)	0.41 (0.29–0.44)	0.03	0.05	
Standard echocardiographic parameters of left ventricular systolic function						
Fractional shortening %	37.00 (32.00-4.002)	36.00 (28.00–39.00)	34.00 (29.50–38.00)	0.43	0.18	37.5 (34.92–39.75)
Ejection fraction %	62.5 (58-70)	60.00 (55.00–64.25)	62.00 (54.00–66.00)	0.64	0.87	64.0 (59.0–69.0)
2D-speckle tracking echocardiographic parameters of left ventricular function						
Peak GLS (%)	−18.8 (−16.5 - −22.5)	−16.85 (−21.14- −15.60)	−13.35 (−17.85– −12.50)	0.01	0.01	−22.3 (−24.93– −19.50)
Peak systolic GLSR (1/s)	−1.1 (−0.9 - −1.2)	−0.95 (−1.20– −0.90)	−0.85 (−1.15– −0.80)	0.06	0.11	−1.20 (−1.40– −1.04)
Peak early diastolic GLSR (1/s)	1.6 (1.2 -2.1)	1.50 (1.10–1.70)	1.20 (0.70–1.60)	0.02	0.02	1.61 (1.55–1.75)
Peak late diastolic GLSR (1/s)	0.6 (0.2 -0.8)	0.50 (0.39–0.70)	0.50 (0.30–0.70)	0.64	0.24	0.77 (0.56–0.92)

Values are median (25 th– 75 th percentile).

Normal Pediatric Values, these normal pediatric values represent the 25-75 percentile strain and strain rate values in a normal healthy age (14 to 18 years) and gender matched pediatric cohort (n = 51) from our echocardiography laboratory. The values are similar to the reference values reported in a separate large pediatric population by Lorch et al 2008. (−22.7±6.5%) Echo, echocardiographic; LVMI, left ventricle mass index; RWT; relative wall thickness; GLS, global longitudinal strain; GLSR, global longitudinal strain rate.