Published in final edited form as:

J Pediatr. 2013 June ; 162(6): 1160–1168.e1. doi:10.1016/j.jpeds.2012.11.024.

Alterations in Ventricular Structure and Function in Obese Adolescents with Nonalcoholic Fatty Liver Disease

Gautam K. Singh, MD^{1,2}, Bernadette E. Vitola, MD, MPH^{1,2}, Mark R. Holland, PhD^{1,3}, Timothy Sekarski, RDCS², Bruce W. Patterson, PhD¹, Faidon Magkos, PhD¹, and Samuel Klein, MD¹

¹Center for Human Nutrition and Atkins Center of Excellence in Obesity Medicine, Washington University School of Medicine, St. Louis, MO

²Department of Pediatrics, Washington University School of Medicine, St. Louis, MO

³Department of Physics, Washington University School of Medicine, St. Louis, MO

Abstract

Objective—To determine the association among nonalcoholic fatty liver disease (NAFLD), metabolic function, and cardiac function in obese adolescents.

Study design—Intrahepatic triglyceride (IHTG) content (magnetic resonance spectroscopy), insulin sensitivity and β -cell function (5-hour oral glucose tolerance test with mathematical modeling), and left ventricular (LV) function (speckle tracking echocardiography) were determined in three groups of age, sex, and Tanner matched adolescents: 1) lean ($n=14$, BMI=20 $\pm$ 2 kg/m²); 2) obese with normal (2.5%) IHTG content ($n=15$, BMI=35 $\pm$ 3 kg/m²); and 3) obese with increased (8.7%) IHTG content ($n=15$, BMI=37 $\pm$ 6 kg/m²).

Results—The disposition index (β -cell function) and insulin sensitivity index (ISI) were ~45% and ~70% lower, respectively, and whole body insulin resistance (HOMA-IR) was ~60% greater, in obese than in lean subjects, and ~30% and ~50% lower and ~150% greater, respectively, in obese subjects with NAFLD than those without NAFLD ($P<0.05$ for all). LV global longitudinal systolic strain and early diastolic strain rates were significantly decreased in obese than in lean subjects, and in obese subjects with NAFLD than those without NAFLD ($P<0.05$ for all), and were independently associated with HOMA-IR ($\beta = 0.634$). IHTG content was the only significant independent determinant of ISI ($\beta = -0.770$), disposition index ($\beta = -0.651$), and HOMA-IR ($\beta = 0.738$).

Conclusions—These findings demonstrate that the presence of NAFLD in otherwise asymptomatic obese adolescents is an early marker of cardiac dysfunction.

Keywords

Nonalcoholic Fatty Liver Disease; Insulin Resistance; Childhood Obesity; Ventricular Function; Heart Structure

© 2012 Mosby, Inc. All rights reserved.

Corresponding author: Samuel Klein, M.D., Center for Human Nutrition, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8031, St Louis, MO 63110, Phone: (314) 3628708, Fax: (314) 3628230, sklein@dom.wustl.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare no conflicts of interest.

Nonalcoholic fatty liver disease (NAFLD) is a common co-morbidity of obesity. The marked increase in the prevalence rate of obesity in the last 30 years¹ has made NAFLD the most common liver abnormality in both children and adults. The prevalence rate of NAFLD in adults increases with increasing body mass index (BMI), from approximately 15% in non-obese persons, to 65% in persons with class I and II obesity (BMI 30.0–39.9 kg/m²), to 85% in extremely obese people (BMI ≥ 40 kg/m²).² The prevalence rate of NAFLD is also high among the obese pediatric population, and approximately one-third of obese children, aged 2–19 years old, have NAFLD.³

The presence of NAFLD also has important implications regarding cardiovascular health. The presence of NAFLD is associated with metabolic abnormalities that are risk factors for coronary heart disease (CHD), such as multi-organ insulin resistance, dyslipidemia, impaired flow-mediated vasodilation and increased carotid-artery intimal medial thickness,^{5–9} and is an important risk factor for CHD.^{10, 11} Data from studies conducted in adult subjects have found that NAFLD is associated with cardiac dysfunction, manifested as myocardial insulin resistance,¹² altered cardiac energy metabolism,¹³ abnormal left ventricular structure and impaired diastolic function.^{14, 15} The duration and severity of these abnormalities are likely important contributors to the increased risk of heart failure and cardiovascular mortality observed in obese people.^{16, 17} Because obesity in adolescence tracks into adulthood,¹⁸ a better understanding of the interrelationship among NAFLD, obesity and cardiac function in adolescents has important physiological and clinical long-term implications.

The purpose of the present cross-sectional study was to test the hypothesis that NAFLD in obese adolescents is associated with early evidence of myocardial structural and functional abnormalities, independent of adiposity and BMI.

METHODS

Three groups of adolescents were studied: (1) lean (n=14); (2) obese (BMI ≥ 95th percentile for age and sex¹⁹) with normal intrahepatic triglyceride (IHTG) content (<5.6% liver volume as triglyceride;²⁰ n=15); and (3) obese with increased IHTG (NAFLD) (≥ 5.6% liver volume as triglyceride; n=15). A comprehensive assessment was made of: (1) body composition, including body fat mass, abdominal fat distribution, and ectopic fat (intrahepatic triglyceride [IHTG], intracardiac triglyceride [ICTG], and skeletal muscle intramuscular triglyceride [IMTG]) by using dual-energy x-ray absorptiometry (DXA), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS); (2) myocardial structure and function by using integrated backscatter ultrasonography and speckle tracking echocardiography (STE); and (3) insulin sensitivity and β -cell function by using a 5-hour frequently sampled oral glucose tolerance test (FSOGTT).

Subjects were recruited from St. Louis Children's Hospital outpatient Preventive Cardiology and Gastroenterology clinics. A total of 44 adolescents out of 57 screened subjects were selected based on inclusion and exclusion criteria. There are no specific criteria to define steatosis or NAFLD by using MRS in children and adolescents. Therefore, we used the cut-off value derived from the Dallas Heart Study conducted in adults.²¹ This value is consistent with the standard histological definition of steatosis (≥ 5% of hepatocytes containing triglyceride) which has been used to diagnose NAFLD in studies conducted in children and adolescents.³ The three groups were matched (one-to-one basis) on age and Tanner stage, and obese adolescents with NAFLD were matched as closely as possible on BMI Z-score with obese adolescents without NAFLD (Table I). All subjects underwent a comprehensive medical evaluation as part of standard of care, which included a detailed history,

questionnaires to screen for obstructive sleep apnea,^{22, 23} physical examination, and routine blood tests (comprehensive metabolic panel, lipid profile, thyroid panel, serology panel, complete blood count, and erythrocyte sedimentation rate). This evaluation helped rule out several other causes of fatty liver, including chronic viral hepatitis, autoimmune hepatitis, hypothyroidism, and genetic defects in lipoprotein metabolism. However, a liver biopsy was not performed in our study subjects so we cannot definitively exclude other potential causes of liver disease, and we did not evaluate surrogate diagnostic serum markers of liver fibrosis, oxidative stress, or apoptosis.²⁴ A 12-lead electrocardiogram and a pregnancy test in female subjects were performed. A 2-hour OGTT was performed in those who had a fasting blood glucose ≥ 100 mg/dl. Subjects who had diabetes, severe hypertriglyceridemia (>350 mg/dl), liver disease other than NAFLD, positive pregnancy test, poor echocardiographic acoustic window and suspected sleep apnea were excluded. None of the subjects consumed >10 g/day of alcohol, smoked tobacco products, took medications known to cause steatosis or affect metabolism, or participated in regular exercise (defined as >1 hour of structured moderate-to-vigorous physical activity per week for the previous 6 months).

The study was approved by the Human Research Protection Office of Washington University School of Medicine in St. Louis, MO. All subjects agreed to participate in the study after a detailed explanation of the study was provided to them and their parents. Written informed consent was obtained from each subject's parent(s) and written informed assent was obtained from each subject before being enrollment.

Body composition analyses, cardiac structure and function studies and assessment of metabolic function were performed in the Center for Clinical Imaging Research, the Echocardiography Laboratory, and the Clinical Research Unit of Washington University School of Medicine on separate days, within a 7-day period. Subjects were studied as outpatients after they fasted for 12 hours overnight before each visit.

Body composition analyses

Body fat mass and fat-free mass were determined by using DXA (Hologic QDR 4500, Waltham, MA). Subcutaneous abdominal and intra-abdominal fat volumes were determined by using MRI with a 1.5 T scanner (Siemens, Iselin, NJ). Eight 10-mm thick axial images were obtained beginning at the L₄-L₅ interspace, and analyzed for subcutaneous and intra-abdominal fat content by using Analyze 6.0 software (Mayo Foundation, Biomedical Imaging Resource, Rochester, MN); the volume of fat was calculated for each slice and the values were added. The amount of triglyceride in the liver (IHTG), soleus muscle (IMTG) and the heart (ICTG) was determined by using MRS (1.5 Tesla MAGNETOM Sonata whole body system, Siemens Medical Systems, Erlangen, Germany), as described previously.^{25, 26}

Cardiovascular structure and function

Blood pressure and heart rate—Systolic and diastolic blood pressures were determined by using oscillometry with appropriate cuff size (two-third relative to arm circumference and length), and heart rate was determined by using auscultation. Three measurements were obtained after 5 min of rest in the sitting position and the median was calculated.

Left ventricle (LV) volume and mass and relative posterior wall thickness—A transthoracic complete 2D and Doppler echocardiographic examination (GE Vivid 7™ ultrasonic imaging system with a M3S phased array transducer, General Electric Medical Systems, Waukesha, WI, USA) was used to determine LV end-diastolic volume, end-systolic volume, and mass according to the recommendations of the American Society of

Echocardiography.²⁷ Left ventricular mass was indexed to height in the power of 2.7.²⁸ The LV end-diastolic and end-systolic volumes were measured by using the modified Simpson method, and LV ejection fraction was calculated as (LV end-diastolic volume minus LV end-systolic volume) / LV end-diastolic volume.²⁹ Relative wall thickness (RWT) of the LV was calculated as the ratio of $2 \times$ posterior wall thickness at end-diastole / LV end-diastolic diameter.

Global myocardial strain and strain rate—Global ventricular function was evaluated by measuring LV strain and strain rate. Strain is a dimensionless measure of myocardial deformation, which is usually reported as percentage change with negative connotation, with more negative values indicating greater strain. Strain rate, a time derivative of strain, correlates linearly with LV peak elastance, which is a load-independent global measure of ventricular systolic function.³⁰ These quantitative measures may precede and are more robust and sensitive than conventional load-dependent indices of cardiac functional changes such as ejection fraction.³¹ Longitudinal strain in pediatric age is relatively independent of maturational changes and normal values in pediatric subjects have been established, taking into consideration the effects of growth, maturation, and body size.³² Myocardial strain in two dimensions is measured by a novel echocardiographic method that determines myocardial deformation from continuous frame-by-frame tracking of speckles.^{31, 33, 34} Speckle tracking echocardiography (STE) is angle-independent, can track in two and three dimensions, and therefore, can assess the magnitude and timing of regional and global ventricular deformation in different directions. Global LV longitudinal, circumferential and radial strain and strain rate were obtained by using two-dimensional STE and quantified by using the EchoPac™ software package (General Electric Medical Systems, Waukesha, WI).^{31, 35}

Myocardial tissue characterization—Cyclic variation of backscatter was used to assess the structural characteristics of myocardial tissue. The principle for using this procedure is based on the known quantitative relationships between ultrasonic backscatter signals and the inherent properties of myocardial tissue.^{36–39} Data from studies have illustrated regional dependence of backscattered ultrasound on intrinsic myofiber organization⁴⁰ and increases in both the measured ultrasonic attenuation and backscatter correlate well with increased collagen concentration.^{36, 41} Cyclic variation of backscatter data was determined in each subject by measuring the mean backscatter value within a region of interest in the posterior wall of the LV in the parasternal long axis view for each image frame recorded over the acquired heart cycles. Cyclic variation of backscatter data was characterized by its magnitude and normalized time delay relative to the systolic interval.^{40, 42}

We have defined myocardial dysfunction as an alteration in LV structure or function that is different from values observed in healthy lean subjects.

Metabolic function

Beta-cell function and insulin sensitivity were evaluated by using a 5-h FSOGTT. An intravenous catheter was placed into an antecubital vein, which was heated by using a thermostatically controlled box, to obtain arterialized venous samples. At time 0, participants ingested 75 g of glucose. Blood samples were collected 10 min before and immediately before ($t=0$) ingesting the glucose load and then at 10, 20, 30, 60, 90, 120, 150, 180, 240, and 300 min after glucose ingestion to determine plasma glucose, insulin, and C-peptide concentrations. Plasma glucose was measured immediately by using an automated glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin and C-peptide were measured by using a chemiluminescent immunoassay (Immulin 1000, Diagnostic Products Corporation, Los Angeles, CA).

Calculations—The total areas under the curve (AUC) for glucose and insulin were calculated by using the trapezoid rule. Whole-body insulin resistance was calculated by using the homeostasis model assessment of insulin resistance (HOMA-IR).⁴³ The insulin sensitivity index (ISI) was estimated from plasma glucose and insulin concentrations obtained during the FSOGTT, by using the oral glucose minimal model.⁴⁴

Beta-cell function was assessed from plasma glucose and C-peptide concentrations obtained during the FSOGTT, by using the oral minimal model of C-peptide secretion and kinetics⁴⁵ and incorporating published parameters for C-peptide kinetics and volume of distribution.⁴⁶ This model provides a global index of postprandial insulin secretion in response to ingested glucose (overall responsivity, Φ_o). The disposition index (DI) was calculated by multiplying the index of global β -cell responsivity (Φ_o) by insulin sensitivity (ISI) to determine insulin secretion in relationship to the degree of insulin resistance.⁴⁷

Statistical Analyses

All datasets were tested for normality according to the Shapiro-Wilks criteria, and non-normally distributed variables were ranked for analysis. Differences among groups in anthropometric characteristics, body composition, metabolic variables, hemodynamic variables, cardiac structure (LV mass, RWT, and measures of the cyclic variation of backscattered energy) and function (EF, global strain and strain rate) were evaluated by using one-way ANOVA, with two planned contrasts for the comparisons of interest: obesity (lean vs. all obese adolescents) and NAFLD (obese adolescents with NAFLD vs. obese adolescents without NAFLD). Differences among groups in frequencies (sex and race) were evaluated by using the χ^2 test. Pearson correlation and stepwise multiple linear regression analyses were performed to assess the relationships between variables of interest. A *P*-value <0.05 was considered significant. All statistical analyses were conducted with SPSS version 19 (IBM SPSS, Chicago, IL).

RESULTS

Body composition

Obese subjects with and without NAFLD were matched on BMI, BMI Z-score and percent body fat (Table I). Intra-abdominal fat volume and IHTG content were greater in obese subjects with NAFLD than those without NAFLD. Although IHTG content was greater in obese subjects with NAFLD than those without NAFLD, IMTG and ICTG were not different between the two groups (Table I). Values for IHTG content correlated positively with percent body fat ($r = 0.570$, $P < 0.001$) and intra-abdominal fat volume ($r = 0.743$, $P < 0.001$), and less strongly with IMTG ($r = 0.345$, $P = 0.027$) and ICTG ($r = 0.363$, $P = 0.020$).

Metabolic function

Fasting plasma glucose concentration and glucose AUC during the FSOGTT were not significantly different among groups, but fasting plasma insulin and C-peptide concentrations and insulin AUC were significantly greater in obese than lean adolescents, and in obese adolescents with NAFLD than those without NAFLD (Table II). The β -cell response to the oral glucose load (Φ_o) was greater, but insulin secretion adjusted for insulin sensitivity (disposition index) was lower, in obese than in lean subjects, and in obese subjects with NAFLD than those without NAFLD (Table II). Whole-body insulin resistance (HOMA-IR) was greater, and insulin sensitivity (ISI) was lower, in obese than in lean subjects, and in obese subjects with NAFLD than those without NAFLD (Table II). Although plasma alanine aminotransferase concentrations were greater in obese than in lean

adolescents and tended to be greater in obese adolescents with NAFLD than those without NAFLD, mean values were within the normal range in all groups (Table II).

β -cell responsivity (Φ_o) was positively correlated and the disposition index was negatively correlated with IHTG content (Figure 1, A and B; available at www.jpeds.com), percent body fat ($r = 0.515$ and $r = -0.440$, respectively; $P < 0.005$), and intra-abdominal adipose tissue volume ($r = 0.632$ and $r = -0.502$, respectively; $P = 0.001$). The ISI was negatively correlated and HOMA-IR score was positively correlated with IHTG content (Figure 1, C and D), percent body fat ($r = -0.629$ and $r = 0.613$, respectively; $P < 0.001$), and intra-abdominal adipose tissue volume ($r = -0.659$ and $r = 0.651$, respectively; $P < 0.001$). Values for ICTG did not correlate with any indices of β -cell function or insulin sensitivity. In multiple stepwise regression analysis with age, Tanner stage, percent body fat, and intra-abdominal adipose tissue volume as predictive variables, IHTG content was the only significant independent determinant of ISI ($\beta = -0.770$), HOMA-IR ($\beta = 0.738$), overall β -cell responsivity Φ_o ($\beta = 0.682$) and disposition index ($\beta = -0.651$) (all $P < 0.001$). However, body composition variables are often highly correlated with each other, which makes it difficult to reliably separate one candidate from another.

Cardiovascular structure and function

Systolic and diastolic blood pressures were greater in obese than lean subjects and in obese subjects with NAFLD than those without NAFLD (Table III). The LV mass and LV mass index were greater in obese than in lean subjects, but were still within the normal range⁴⁸ and were not different between obese subjects with and without NAFLD. Relative posterior wall thickness was not significantly different among groups and was normal for age (< 0.41 ^{48, 49}) in most subjects; two obese adolescents with NAFLD, who had RWT values of 0.43 and 0.44 (Table III). No significant differences among groups were detected in the magnitude of cyclic variation of backscatter, but there was a trend of increasing normalized time delay of cyclic variation of backscatter in obese compared with lean subjects (Table III).

The LV global longitudinal strain was significantly decreased in obese than in lean subjects and in obese subjects with NAFLD than those without NAFLD (Figure 2 and Table III), indicating greater systolic dysfunction in the NAFLD group. Compared with lean adolescents, the obese groups had decreased systolic and early diastolic longitudinal strain rates. Early diastolic longitudinal strain rates were significantly decreased in obese subjects with NAFLD than those without NAFLD (Figure 2 and Table III), indicating greater diastolic dysfunction in the NAFLD group. The LV ejection fraction was normal and similar among the three groups.

The LV global longitudinal strain and systolic and early diastolic strain rates correlated positively with IHTG content ($r = 0.25$ – 0.40 , $P < 0.05$), percent body fat ($r = 0.30$ – 0.40 , $P < 0.05$), and intra-abdominal adipose tissue volume ($r = 0.40$ – 0.60 , $P < 0.05$), but not ICTG (all $P > 0.55$). In multiple stepwise regression analysis with age, Tanner stage, BMI, blood pressure, percent body fat, intra-abdominal adipose tissue volume, total cholesterol and LDL-cholesterol, IHTG content, and insulin sensitivity and β -cell function indices as predictive variables, the HOMA-IR score was the only independent variable associated with global longitudinal strain ($\beta = 0.634$, $P < 0.001$), global longitudinal systolic strain rate ($\beta = 0.487$, $P = 0.001$), and longitudinal early diastolic strain rate ($\beta = 0.527$, $P = 0.001$). IHTG content did not significantly contribute further to explaining the variance in these measures of myocardial function.

DISCUSSION

The presence of increased IHTG content is an important marker of metabolic dysfunction (multi-organ insulin resistance and dyslipidemia).^{5, 6} Our data demonstrate that obese adolescents with NAFLD have greater abnormalities in cardiac function, manifested by decreased systolic and diastolic myocardial strain and strain rate than obese adolescents who have normal IHTG content. The cardiac functional abnormalities in our obese adolescents with NAFLD were independent of traditional cardiac risk factors (i.e. high systolic and diastolic blood pressures, total and LDL cholesterol, and BMI), and correlated with insulin resistance. Furthermore, insulin sensitivity was decreased in obese adolescents with NAFLD compared with those without NAFLD, as shown previously in obese adults.^{7, 8} In addition, increased IHTG content was associated with increased insulin secretion in response to ingested glucose, which has also been shown previously in adults with NAFLD.^{50–52} However, the disposition index, which provides a more comprehensive assessment of β -cell function (i.e. insulin response to glucose in relationship to the degree of insulin resistance) was lower in obese adolescents with NAFLD than in those without NAFLD. Therefore, our findings demonstrate that the presence of NAFLD in obese adolescents is an early marker of myocardial dysfunction, and support the notion that NAFLD is an integral component of the cardiometabolic abnormalities that increase the risk of future diabetes and congestive heart failure in obese children.

The precise mechanism responsible for the link between IHTG content and myocardial dysfunction cannot be determined from our study. Although all our obese subjects were clinically asymptomatic and had a normal ejection fraction, they demonstrated evidence of impaired systolic and diastolic function manifested by decreased LV systolic strain, strain rate, and early diastolic rate. These alterations in myocardial function were worse in obese adolescents with NAFLD than in those with normal IHTG content. The abnormalities in cardiac function observed in our obese subjects likely involve myocardial fiber organization that affects ventricular intrinsic deformation, which we measured with the relatively load-independent parameters of strain and strain rate. These results indicate that conventional measures of cardiac function, which are load dependent, do not provide a sensitive assessment of early stages of cardiac dysfunction. Data from another study in obese children and adolescents, employing strain and strain rate measurements by 3D-wall motion tracking echocardiography, also demonstrated abnormal myocardial deformation changes.⁵³ Increased blood pressure can affect myocardial deformation,⁵⁴ and our obese subjects had higher systolic and diastolic blood pressure values than our lean subjects. Myocardial deformational changes caused by high blood pressure vary according to the LV adaptive response, manifested by abnormalities in LV mass and RWT. The adaptive response with normal geometry has normal deformation and other adaptive responses have abnormal deformation. It is thus unlikely that differences in blood pressure contributed to differences in myocardial function among our study groups, because all our subjects had LV mass below the 95th percentile and all but two obese subjects with NAFLD had RWT values that were within the normal range,^{48, 49} indicating normal LV geometry (normal RWT and LV mass) with no signs of concentric remodeling), concentric hypertrophy (increased RWT, increased LV mass), or eccentric hypertrophy (decreased RWT, increased LV mass).^{55–57} In addition, regression analysis found the impairment in ventricular function was independent of blood pressure.

In contrast with data reported from studies conducted in adult subjects,^{20, 58} we found that impaired cardiac function was not accompanied by an increase in ICTG content. Although we cannot exclude a type II error, this result suggests that asymptomatic alterations in cardiac function in our obese adolescents represent an early stage in the cascade of events, presumably induced by alterations in myocardial energy metabolism, which preceded ICTG

accumulation. However, cardiac dysfunction was associated with insulin resistance, suggesting that an insulin resistance-induced increase in myocardial fatty acid uptake⁵⁹ causes both an impairment in cardiac function and an accumulation of ICTG. Given the tendency for obesity to track from adolescence into adulthood,¹⁸ persistence of these metabolic disturbances can lead to progressive structural remodeling of the heart as suggested by increasing normalized time delay of cyclic variation of backscatter and obesity-associated cardiomyopathy.⁶⁰

The presence of NAFLD in obese adolescents is associated with cardiac ventricular dysfunction, independent of BMI, conventional cardiovascular risk factors, and ICTG content. In addition, IHTG content itself is associated with β -cell dysfunction and insulin resistance which are likely involved in the pathogenesis of obesity-related myocardial dysfunction. These results demonstrate that NAFLD should be considered part of the constellation of metabolic and myocardial abnormalities in obese adolescents that increase their risk for developing type 2 diabetes and heart failure. Determining the specific criteria needed to optimize the stratification of cardiovascular risk in obese adolescents requires more research, including a careful assessment of NAFLD severity.

Acknowledgments

The authors thank the staff of the Clinical Research Unit for their help in performing the studies, and the study subjects for their participation.

Supported by National Institutes of Health (DK 37948, DK 56341 [Nutrition Obesity Research Center], and RR024992 [Clinical and Translational Science Award]).

Abbreviations and Acronyms

AUC	area under the curve
BMI	body mass index
CHD	coronary heart disease
FSOGTT	frequently sampled oral glucose tolerance test
HOMA-IR	homeostasis model assessment
ICTG	intracardiac triglyceride
IHTG	intrahepatic triglyceride
IMTG	skeletal muscle intramuscular triglyceride
ISI	insulin sensitivity index from minimal modeling
LV	left ventricle
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
STE	speckle tracking echocardiography

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults 1999–2000. *JAMA*. 2002; 288:1723–1727. [PubMed: 12365955]
2. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology*. 2010; 51:679–689. [PubMed: 20041406]

3. Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics*. 2006; 118:1388–1393. [PubMed: 17015527]
4. Brunt EM. Nonalcoholic steatohepatitis: definition and pathology. *Semin Liver Dis*. 2001; 21:3–16. [PubMed: 11296695]
5. Deivanayagam S, Mohammed BS, Vitola BE, Naguib GH, Keshen TH, Kirk EP, et al. Nonalcoholic fatty liver disease is associated with hepatic and skeletal muscle insulin resistance in overweight adolescents. *Am J Clin Nutr*. 2008; 88:257–262. [PubMed: 18689359]
6. Fabbrini E, deHaseth D, Deivanayagam S, Mohammed BS, Vitola BE, Klein S. Alterations in fatty acid kinetics in obese adolescents with increased intrahepatic triglyceride content. *Obesity (Silver Spring)*. 2009; 17:25–29. [PubMed: 18948971]
7. Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, et al. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proc Natl Acad Sci U S A*. 2009; 106:15430–15435. [PubMed: 19706383]
8. Korenblat KM, Fabbrini E, Mohammed BS, Klein S. Liver, muscle, and adipose tissue insulin action is directly related to intrahepatic triglyceride content in obese subjects. *Gastroenterology*. 2008; 134:1369–1375. [PubMed: 18355813]
9. Schwimmer JB, Pardee PE, Lavine JE, Blumkin AK, Cook S. Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. *Circulation*. 2008; 118:277–283. [PubMed: 18591439]
10. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005; 129:113–121. [PubMed: 16012941]
11. Stepanova M, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. *Clin Gastroenterol Hepatol*. 2012; 10:646–650. [PubMed: 22245962]
12. Lautamaki R, Borra R, Iozzo P, Komu M, Lehtimäki T, Salmi M, et al. Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2006; 291:E282–E290. [PubMed: 16478772]
13. Perseghin G, Lattuada G, De Cobelli F, Esposito A, Belloni E, Ntali G, et al. Increased mediastinal fat and impaired left ventricular energy metabolism in young men with newly found fatty liver. *Hepatology*. 2008; 47:51–58. [PubMed: 17955548]
14. Fallo F, Dalla Pozza A, Sonino N, Lupia M, Tona F, Federspil G, et al. Non-alcoholic fatty liver disease is associated with left ventricular diastolic dysfunction in essential hypertension. *Nutr Metab Cardiovasc Dis*. 2009; 19:646–653. [PubMed: 19278843]
15. Goland S, Shimoni S, Zornitzki T, Knobler H, Azoulai O, Lutaty G, et al. Cardiac abnormalities as a new manifestation of nonalcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. *J Clin Gastroenterol*. 2006; 40:949–955. [PubMed: 17063117]
16. Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology*. 2006; 44:865–873. [PubMed: 17006923]
17. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation*. 2004; 110:2952–2967. [PubMed: 15509809]
18. Freedman DS, Khan LK, Dietz WH, Srinivasan SR, Berenson GS. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. *Pediatrics*. 2001; 108:712–718. [PubMed: 11533341]
19. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007; 120(Suppl 4):S164–S192. [PubMed: 18055651]
20. Szczepaniak LS, Dobbins RL, Metzger GJ, Sartoni-D'Ambrosia G, Arbique D, Vongpatanasin W, et al. Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized

- proton spectroscopy and cardiac imaging. *Magn Reson Med*. 2003; 49:417–423. [PubMed: 12594743]
21. Szczepaniak LS, Nurenberg P, Leonard D, Browning JD, Reingold JS, Grundy S, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab*. 2005; 288:E462–E468. [PubMed: 15339742]
 22. Brouillette R, Hanson D, David R, Klemka L, Szatkowski A, Fernbach S, et al. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr*. 1984; 105:10–14. [PubMed: 6737123]
 23. Netzer NC, Hoegel JJ, Loubé D, Netzer CM, Hay B, Alvarez-Sala R, et al. Prevalence of symptoms and risk of sleep apnea in primary care. *Chest*. 2003; 124:1406–1414. [PubMed: 14555573]
 24. Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. *J Pediatr Gastroenterol Nutr*. 2012; 54:700–713. [PubMed: 22395188]
 25. Frimel TN, Deivanayagam S, Bashir A, O'Connor R, Klein S. Assessment of intrahepatic triglyceride content using magnetic resonance spectroscopy. *J Cardiometab Syndr*. 2007; 2:136–138. [PubMed: 17684473]
 26. O'Connor RD, Bashir A, Todd Cade W, Yarasheski KE, Gropler RJ. ¹H-magnetic resonance spectroscopy for quantifying myocardial lipid content in humans with the cardiometabolic syndrome. *J Clin Hypertens (Greenwich)*. 2009; 11:528–532. [PubMed: 19751469]
 27. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. 2010; 23:465–495. [PubMed: 20451803]
 28. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004; 114:555–576. [PubMed: 15286277]
 29. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989; 2:358–367. [PubMed: 2698218]
 30. Greenberg NL, Firstenberg MS, Castro PL, Main M, Travaglini A, Odabashian JA, et al. Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility. *Circulation*. 2002; 105:99–105. [PubMed: 11772883]
 31. Singh GK, Cupps B, Pasque M, Woodard PK, Holland MR, Ludomirsky A. Accuracy and reproducibility of strain by speckle tracking in pediatric subjects with normal heart and single ventricular physiology: a two-dimensional speckle-tracking echocardiography and magnetic resonance imaging correlative study. *J Am Soc Echocardiogr*. 2010; 23:1143–1152. [PubMed: 20850945]
 32. Lorch SM, Ludomirsky A, Singh GK. Maturation and growth-related changes in left ventricular longitudinal strain and strain rate measured by two-dimensional speckle tracking echocardiography in healthy pediatric population. *J Am Soc Echocardiogr*. 2008; 21:1207–1215. [PubMed: 18992672]
 33. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain—a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr*. 2004; 17:1021–1029. [PubMed: 15452466]
 34. Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E, et al. Two-dimensional strain—a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. *J Am Soc Echocardiogr*. 2005; 18:1247–1253. [PubMed: 16376750]
 35. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against

- sonomicrometry and tagged magnetic resonance imaging. *J Am Coll Cardiol.* 2006; 47:789–793. [PubMed: 16487846]
36. Hall CS, Scott MJ, Lanza GM, Miller JG, Wickline SA. The extracellular matrix is an important source of ultrasound backscatter from myocardium. *J Acoust Soc Am.* 2000; 107:612–619. [PubMed: 10641669]
 37. O'Brien WD, Sagar KB, Warltier DC, Rhyne TL. Acoustic propagation properties of normal, stunned, and infarcted myocardium. Morphological and biochemical determinants. *Circulation.* 1995; 91:154–160. [PubMed: 7805196]
 38. Rose JH, Kaufmann MR, Wickline SA, Hall CS, Miller JG. A proposed microscopic elastic wave theory for ultrasonic backscatter from myocardial tissue. *J Acoust Soc Am.* 1995; 97:656–668. [PubMed: 7860840]
 39. Wickline SA, Thomas LJ 3rd, Miller JG, Sobel BE, Perez JE. A relationship between ultrasonic integrated backscatter and myocardial contractile function. *J Clin Invest.* 1985; 76:2151–2160. [PubMed: 3908482]
 40. Holland MR, Wilkenshoff UM, Finch-Johnston AE, Handley SM, Perez JE, Miller JG. Effects of myocardial fiber orientation in echocardiography: quantitative measurements and computer simulation of the regional dependence of backscattered ultrasound in the parasternal short-axis view. *J Am Soc Echocardiogr.* 1998; 11:929–937. [PubMed: 9804097]
 41. Hoyt RM, Skorton DJ, Collins SM, Melton HE Jr. Ultrasonic backscatter and collagen in normal ventricular myocardium. *Circulation.* 1984; 69:775–782. [PubMed: 6697461]
 42. Gibson AA, Schaffer JE, Peterson LR, Bilhorn KR, Robert KM, Haider TA, et al. Quantitative analysis of the magnitude and time delay of cyclic variation of myocardial backscatter from asymptomatic type 2 diabetes mellitus subjects. *Ultrasound Med Biol.* 2009; 35:1458–1467. [PubMed: 19616360]
 43. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985; 28:412–419. [PubMed: 3899825]
 44. Dalla Man C, Caumo A, Basu R, Rizza R, Toffolo G, Cobelli C. Minimal model estimation of glucose absorption and insulin sensitivity from oral test: validation with a tracer method. *Am J Physiol Endocrinol Metab.* 2004; 287:E637–E643. [PubMed: 15138152]
 45. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity. *Diabetes.* 2001; 50:150–158. [PubMed: 11147781]
 46. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes.* 1992; 41:368–377. [PubMed: 1551497]
 47. Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of beta-cell function: the hyperbolic correction. *Diabetes.* 2002; 51(Suppl 1):S212–S220. [PubMed: 11815482]
 48. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. *J Am Soc Echocardiogr.* 2009; 22:709–714. [PubMed: 19423289]
 49. Daniels SR, Loggie JM, Khoury P, Kimball TR. Left ventricular geometry and severe left ventricular hypertrophy in children and adolescents with essential hypertension. *Circulation.* 1998; 97:1907–1911. [PubMed: 9609083]
 50. Rijkkelijkhuizen JM, Doesburg T, Girman CJ, Mari A, Rhodes T, Gastaldelli A, et al. Hepatic fat is not associated with beta-cell function or postprandial free fatty acid response. *Metabolism.* 2009; 58:196–203. [PubMed: 19154952]
 51. Tushuizen ME, Bunck MC, Pouwels PJ, Bontemps S, Mari A, Diamant M. Lack of association of liver fat with model parameters of beta-cell function in men with impaired glucose tolerance and type 2 diabetes. *Eur J Endocrinol.* 2008; 159:251–257. [PubMed: 18583389]
 52. Lattuada G, Ragogna F, Perseghin G. Why does NAFLD predict type 2 diabetes? *Curr Diab Rep.* 2011; 11:167–172. [PubMed: 21431854]
 53. Saltijeral A, Isla LP, Perez-Rodriguez O, Rueda S, Fernandez-Golfin C, Almeria C, et al. Early myocardial deformation changes associated to isolated obesity: a study based on 3D-wall motion tracking analysis. *Obesity (Silver Spring).* 2011; 19:2268–2273. [PubMed: 21720437]

54. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med.* 1991; 114:345–352. [PubMed: 1825164]
55. Kang SJ, Lim HS, Choi BJ, Choi SY, Hwang GS, Yoon MH, et al. Longitudinal strain and torsion assessed by two-dimensional speckle tracking correlate with the serum level of tissue inhibitor of matrix metalloproteinase-1, a marker of myocardial fibrosis, in patients with hypertension. *J Am Soc Echocardiogr.* 2008; 21:907–911. [PubMed: 18325736]
56. Kouzu H, Yuda S, Muranaka A, Doi T, Yamamoto H, Shimoshige S, et al. Left ventricular hypertrophy causes different changes in longitudinal, radial, and circumferential mechanics in patients with hypertension: a two-dimensional speckle tracking study. *J Am Soc Echocardiogr.* 2011; 24:192–199. [PubMed: 21145703]
57. Saltijeral A, Perez de Isla L, Veras K, Fernandez Mde J, Gorissen W, Rementeria J, et al. Myocardial strain characterization in different left ventricular adaptative responses to high blood pressure: a study based on 3D-wall motion tracking analysis. *Echocardiography.* 2010; 27:1238–1246. [PubMed: 20584068]
58. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. *J Am Coll Cardiol.* 2008; 52:1793–1799. [PubMed: 19022158]
59. Peterson LR, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation.* 2004; 109:2191–2196. [PubMed: 15123530]
60. Perseghin G, Ntali G, De Cobelli F, Lattuada G, Esposito A, Belloni E, et al. Abnormal left ventricular energy metabolism in obese men with preserved systolic and diastolic functions is associated with insulin resistance. *Diabetes Care.* 2007; 30:1520–1526. [PubMed: 17384336]

Figure 1. (online). Relationship between intrahepatic triglyceride (IHTG) content and indices of β -cell function and insulin sensitivity in lean adolescents and obese adolescents with and without nonalcoholic fatty liver disease (NAFLD). **A**) Global β -cell responsiveness to oral glucose (Φ_0), **B**) insulin secretion adjusted for insulin sensitivity (disposition index, DI), **C**) insulin sensitivity index (ISI), and **D**) homeostasis model assessment of insulin resistance (HOMA-IR). Data are ranked. All relationships are statistically significant ($P < 0.001$).

Figure 2.

Cardiac function in lean adolescents and obese adolescents with and without nonalcoholic fatty liver disease (NAFLD). **A)** Left ventricular (LV) global strain, **B)** LV longitudinal global strain rate in systole, and **C)** LV longitudinal global strain rate in early diastole. Values are means±SD (A, C) or medians with quartiles (B). * Value significantly different from value in obese subjects ($P < 0.05$), † value significantly different from value in obese subjects without NAFLD ($P < 0.05$).

Table 1

Demographic characteristics and body composition of lean adolescents and obese adolescents with and without nonalcoholic fatty liver disease (NAFLD)

	Lean		Obese		P-values	
	Normal	IHTG	NAFLD	ANOVA	Obesity	NAFLD
Age (yr)	15 (14, 17)	15 (14, 17)	15 (13, 16)	0.937	0.719	1.000
Tanner stage	4 (4, 5)	5 (4, 5)	4 (4, 5)	0.919	0.683	1.000
Sex (Females/Males)	6/8	9/6	6/9	0.497*	–	–
Race (C/AA/A/NA)	12/2/0/0	8/7/0/0	9/4/1/1	0.255*	–	–
Body mass index (kg/m ²)	19.9±1.6	34.5±2.9	37.4±5.9	<0.001	<0.001	0.102
Body mass index Z-score	-0.15±0.52	2.21±0.26	2.41±0.34	<0.001	<0.001	0.174
Body fat (% body weight)	19.5±7.2	39.7±6.1	40.7±5.9	<0.001	<0.001	0.674
Total abdominal fat (cm ³)	1444±684	6387±1623	7613±2244	<0.001	<0.001	0.050
Intra-abdominal fat (cm ³)	203 (165, 269)	680 (536, 785)	1119 (883, 1919)	<0.001	<0.001	<0.001
Subcutaneous abdominal fat (cm ³)	1209±586	5141±1717	6259±1852	<0.001	<0.001	0.050
Intrahepatic triglyceride (%)	1.0 (0.4, 1.9)	2.5 (2.0, 4.0)	8.7 (7.5, 14.5)	<0.001	<0.001	<0.001
Intracardiac triglyceride (%)	0.5 (0.3, 1.1)	0.6 (0.4, 0.8)	0.7 (0.5, 1.5)	0.353	0.303	0.321
Intramuscular triglyceride (%)	0.6 (0.3, 1.0)	1.1 (0.7, 1.3)	1.0 (0.6, 2.3)	0.040	0.013	0.632

Values are mean±SD for normally distributed variables and median (quartiles) for non-normally distributed variables.

P-values are shown for the one-way ANOVA model and the two contrasts tested: *Obesity* (lean vs. all obese adolescents) and *NAFLD* (obese adolescents with NAFLD vs. obese adolescents without NAFLD).

* Sex and race distributions were evaluated by using the χ^2 test.

Abbreviations: IHTG, intrahepatic triglyceride; C, Caucasian; AA, African American; A, Asian; NA, Native American.

Table 2

Metabolic variables in lean adolescents and obese adolescents with and without nonalcoholic fatty liver disease (NAFLD)

	Lean		Obese		P-values	
			Normal IHTG	NAFLD	ANOVA	Obesity
<i>Basal plasma concentrations</i>						
Glucose (mg/dl)	89 (83, 93)		89 (87, 96)	91 (86, 102)	0.283	0.197
Insulin (mU/L)	8 (5, 12)		15 (12, 22)	36 (23, 49)	<0.001	<0.001
C-peptide (pmol/L)	500 (440, 606)		699 (559, 917)	1032 (879, 1352)	<0.001	<0.001
<i>Areas-under-the-curve</i>						
Glucose (mg/dl-min)	32673 (30109, 34474)		31269 (29618, 33466)	32972 (31255, 35816)	0.245	0.932
Insulin (mU/L-min)	13038 (10195, 16597)		16537 (12750, 22844)	43598 (25382, 59409)	<0.001	<0.001
<i>Insulin secretion indices</i>						
Global beta-cell responsiveness, Φ_0	13.1 $\pm$ 3.4		15.4 $\pm$ 5.6	24.4 $\pm$ 7.6	<0.001	0.002
Disposition index	0.0064 $\pm$ 0.0049		0.0041 $\pm$ 0.0028	0.0028 $\pm$ 0.0017	<0.001	<0.001
<i>Insulin sensitivity indices</i>						
Insulin sensitivity index (ISI)	0.0006 $\pm$ 0.0005		0.0003 $\pm$ 0.0002	0.0001 $\pm$ 0.0001	<0.001	<0.001
HOMA-IR score	1.9 (1.2, 2.6)		3.1 (2.6, 4.8)	7.8 (5.5, 10.8)	<0.001	<0.001
<i>Plasma lipids</i>						
Triglyceride (mg/dl)	64 $\pm$ 37		90 $\pm$ 53	122 $\pm$ 70	0.027	0.024
HDL-cholesterol (mg/dl)	45 $\pm$ 9		43 $\pm$ 13	36 $\pm$ 6	0.057	0.136
Total cholesterol (mg/dl)	127 $\pm$ 25		136 $\pm$ 25	165 $\pm$ 42	0.006	0.025
LDL-cholesterol (mg/dl)	69 $\pm$ 20		75 $\pm$ 20	105 $\pm$ 34	0.001	0.017
<i>Hepatic enzymes</i>						
Alanine aminotransferase (U/L)	15 (12, 18)		17 (13, 17)	24 (17, 39)	0.01	0.01
Aspartate aminotransferase (U/L)	22 (19, 27)		20 (19, 24)	23 (21, 26)	0.30	0.96

Values are mean $\pm$ SD for normally distributed variables and median (quartiles) for non-normally distributed variables. P-values are shown for the one-way ANOVA model and the two contrasts tested: *Obesity* (lean vs. all obese adolescents) and *NAFLD* (obese adolescents with NAFLD vs. obese adolescents without NAFLD).

Abbreviations: IHTG, intrahepatic triglyceride; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3

Myocardial structure and function and hemodynamics in lean adolescents and obese adolescents with and without nonalcoholic fatty liver disease (NAFLD)

	Lean	Obese		P-values	
		Normal IHTG	NAFLD	ANOVA	Obesity
Systolic blood pressure (mmHg)	109±11	120±10	127±7	<0.001	<0.001
Diastolic blood pressure (mmHg)	68±5	74±9	79±6	<0.001	<0.001
Heart rate (bpm)	78±9	82±5	83±4	0.084	0.097
RWT	0.29±0.06	0.33±0.04	0.35±0.04	0.070	0.070
LV mass (g)	96±23	115±28	132±28	0.004	0.003
LV mass index (g/m ^{2.7})	24±4	29±5	31±7	0.002	0.001
LV ejection fraction (%)	58.7±4.2	57.4±4.0	59.1±3.9	0.480	0.727
LV longitudinal global strain (%)	-18.2±2.6	-16.6±2.2	-14±3.8	0.002	0.005
LV longitudinal global strain rate in systole (%/s)	-0.97 (-1.08, -0.95)	-0.90 (-0.97, -0.80)	-0.87 (-1.00, -0.65)	0.013	0.001
LV longitudinal global strain rate in early diastole (%/s)	1.58±0.32	1.37±0.22	1.14±0.32	0.001	0.001
LV longitudinal global strain rate in late diastole (%/s)	0.55 (0.44, 0.81)	0.50 (0.37, 0.60)	0.50 (0.43, 0.57)	0.455	0.338
Magnitude of cyclic variation (dB)	4.3±1.7	4.5±1.5	3.7±2	0.460	0.704
Normalized time delay of cyclic variation	0.8 (0.5, 1.03)	0.92 (0.64, 1.95)	1.0 (0.62, 2.31)	0.247	0.097

Values are mean±SD for normally distributed variables and median (quartiles) for non-normally distributed variables.

P-values are shown for the one-way ANOVA model and the two contrasts tested: *Obesity* (lean vs. all obese adolescents) and *NAFLD* (obese adolescents with NAFLD vs. obese adolescents without NAFLD).

Abbreviations: IHTG, intrahepatic triglyceride; RWT, relative posterior wall thickness; LV, left ventricular.