Early Left Ventricular Systolic Dysfunction Detected by Two-Dimensional Speckle-Tracking Echocardiography in Young Patients with Congenital Generalized Lipodystrophy

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Purpose: Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disorder characterized by the absence of functional adipocytes resulting in ectopic lipid storage, metabolic disorders and early cardiovascular disease. Two-dimensional speckle-tracking (2D-STE) allows the detection of early abnormalities in myocardial function. We aimed to evaluate myocardial deformation in a large sample of CGL patients using 2D-STE.

Patients and Methods: A cross-sectional study of 22 patients with CGL and 22 healthy subjects, matched for sex and age, was conducted from 2013 to 2018. All participants had undergone standard conventional echocardiography (ECHO) and 2D-STE. Determination of blood glucose, lipids, insulin, and leptin were performed in all CGL patients.

Results: In the CGL group the mean age was 14.6 ± 10.7 years where 68.2% (n=15) were younger than 18 years old. All the patients had hypoleptinemia, 95.4% (21/22) low HDL-c, 86.4% (19/22) hypertriglyceridemia, 68.2% (15/22) diabetes, 50% (11/22) hepatic steatosis, 41% (9/22) insulin resistance, 41% (9/22) hypercholesterolemia, and 18.2% (4/22) hypertension. ECHO showed that 36.6% (8/22) of CGL patients presented diastolic dysfunction, 31.8% (7/22) left ventricular hypertrophy (LVH), 27.3% (6/22) increased left atrial volume index (LAVI), and 18.2% (4/22) increased left ventricular systolic diameter (LVDS) but normal ejection fraction (EF), whether using 2D-STE, 68.2% (15/22) of CGL patients showed abnormal global longitudinal strain (GLS) ($p < 0.01$), and in almost LV segments. Positive association between abnormal GLS and A1c ($r = 0.57$, $p = 0.005$), glucose ($r = 0.5$, $p = 0.018$) and basal insulin ($r = 0.69$, $p = 0.024$), and negative association with leptin ($r = -0.51$, $p = 0.005$) were found in these patients.

Conclusion: The 2D-STE revealed precocious left ventricular systolic dysfunction in a young CGL population with normal systolic function by ECHO. Early exposure to common metabolic abnormalities as insulin resistance, hyperglycemia, and hypoleptinemia must be involved in myocardial damage in these patients.

Keywords: Berardinelli-Seip congenital lipodystrophy, global longitudinal strain, cardiac function, early detection

Introduction

Congenital Generalized Lipodystrophy (CGL) is a rare autosomal recessive disease with a higher incidence in countries such as Lebanon, Portugal, Oman and Brazil. The absence of subcutaneous adipose tissue since birth or early childhood and consequent impairment of normal fat deposition lead to precocious ectopic lipid accumulation in tissues such as muscle, liver, heart and arterial wall. Consequently,

there are severe and precocious metabolic abnormalities as insulin resistance, diabetes mellitus, hepatic steatosis and premature atherosclerotic disease, which may lead to early cardiovascular mortality.^{1,2}

Cardiomyopathy, heart failure, systemic arterial hypertension, myocardial infarction, arrhythmias and sudden death have been described in CGL.^{3–5} The evaluation of heart morphology and function in this population has been performed by conventional echocardiography (ECHO). Although ECHO is the most common approach for assessing left ventricular (LV) systolic function mainly based on ejection fraction (EF), this is limited in detecting subtle abnormalities in myocardial contraction.⁶

Two-dimensional speckle-tracking echocardiography (2D-STE) is a new echocardiography technique that plays an important role in early detection of cardiac dysfunction, and more sensitive than EF to evaluate LV systolic function.^{7–11} The 2D-STE measures myocardial deformation through the measurement of global longitudinal strain (GLS), global circumferential strain (GCS) or global radial strain (GRS).^{6,10}

Few studies have assessed cardiac function in patients with CGL, mainly case reports, and none using 2D-STE.^{3,12–17} Thus, the aim of this study was to assess myocardial deformation and detect preclinical myocardial dysfunction using 2D-STE echocardiography in a large sample of patients with generalized congenital lipodystrophy.

Materials and Methods

Study Population

This is a cross-sectional study of CGL patients from Ceará, Northeast of Brazil, conducted from January 2013 to December 2018. Patients were followed up by a multidisciplinary team of the regional reference center of the Brazilian Group for the Study of Inherited and Acquired Lipodystrophies (BRAZLIPO).

The current study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.¹⁸

The inclusion criteria were CGL diagnosed according to the clinical criteria by Patni e Garg.¹⁹ Exclusion criteria were: unstable sinus rhythm, conduction and rhythm disorders, and poor acoustic windows. Patients who did not complete the study protocol were excluded.

The control group consisted of healthy and eutrophic individuals matched 1:1 according to age and gender. Healthy individuals were those without diabetes or any other metabolic disease, did not use any medication, and

did not present any episode of infection or hospitalization in the last month. Exclusion criteria were the same used for the group of patients.

Clinical and Biochemical Analysis

Clinical history was assessed through medical records, and physical examination and anthropometric measurements were performed on all the participants. In CGL group, biochemical tests were carried out after a 12 hr fasting to determine blood glucose, total cholesterol, HDL-cholesterol, triglycerides, glycohemoglobin A1c (A1c), basal insulin and leptin. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated in patients who did not use exogenous insulin.²⁰ Genetic testing was performed according to the previous study.²¹

Echocardiography Analysis

Standard transthoracic echocardiography study was performed using Vivid 7 and Vivid 9 (GE Medical Systems, Milwaukee, Wisconsin®, USA) ultrasound machines with a 3.5-MHz transducer for harmonic imaging following the criteria established by the American Society of Echocardiography.^{22–25}

Conventional Echocardiography

The values of all conventional ECHO parameters were calculated as the average value of three consecutive cardiac cycles. LV end-systolic and end-diastolic diameters, LV posterior wall and interventricular septum thickness were measured using the two-dimensional echocardiography guided M-mode method. Measurements were analyzed according to the reference values; therefore, the participants were divided into age groups: children and adolescents (<18 years of age) and adults (≥18 years of age).²⁶ Left ventricle ejection fraction (LVEF) was estimated using the Simpson method. LV mass was calculated using the Devereaux formula and indexed to the height in children and adolescents^{2,8} and to the body surface area (BSA) in adults.^{26–28}

Pulsed-wave Doppler (PW) was used to measure mitral inflow velocities, peak early (E) and late (A) diastolic velocities, the E/A ratio, and the E-wave deceleration time. The early diastolic velocity (E') of the mitral annulus was measured at the lateral (El) and septal (Es) sites of the mitral annulus using pulsed-wave Doppler tissue imaging (DTI). The average E' value (lateral and septal sites) was used to calculate the E/E' ratio.²⁹ Left atrial volume (LAV) was calculated using the biplane disk summation technique and then

indexed to the BSA.³⁰ In addition, Color Doppler flow imaging was used for mapping valvar regurgitation.

Speckle Tracking Echocardiography

To obtain specific 2D images using STE, digital loops with three successive cardiac cycles were acquired from LV apical 2-chamber (2C), 3-chamber (3C) and 4-chamber (4C) views. The frame rate for these recordings was set at 60 to 90 frames/s.^{31,32} After selecting the best-quality two-dimensional image of the cardiac cycle, the LV endocardial border was manually traced at the end-systolic frame. After that, a speckle-tracking region of interest was automatically selected to approximate the myocardium between the endocardium and epicardium. The width of the region of interest was adjusted as necessary to accommodate the total thickness of the LV wall. The LV was divided into 18 segments: 3 levels (basal, mid-cavity and apical), which were further divided into 6 segments (anterior, posterior, lateral, inferior, septal, and anteroseptal). Longitudinal strains for each individual segment were measured and expressed as a bull's-eye, and the software calculated GLS by averaging local strains along the entire LV.^{33,34} More negative strain values represent an increased contraction of the myocardium. Normal values of GLS were stratified by age distribution (years) according to references ranges.^{30,35}

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (GraphPad Software Inc., San Diego, CA, USA). Descriptive analysis was presented in tables with frequency and percentage for categorical variables and mean and standard deviation for numerical variables. Fisher's exact test, Pearson's chi-squared test and Spearman correlation coefficient were used to check for associations between the studied variables. Student's *t*-test or Mann-Whitney test were used to compare means. The normality of data was tested using the Shapiro-Wilk test. A *p*-value < 0.05 was considered statistically significant.

Results

Clinical and Metabolic Characteristics of the CGL Group

Twenty-two patients with a clinical diagnosis of CGL were evaluated. The mean age was 14.6±10.7 years, 68.2% (15/22) were younger than 18 years old, and 59% (13/22) were women. The mean age of participants in the group <18 years was 8.3±4.7 years, and in the group ≥ 18 years was 28.0±6.2 years. The mean age at CGL diagnosis was 7.4±11.1 years, ranging from 1

month to 38 years of age. All the patients had hypoleptinemia, 95.4% (21/22) had low HDL-c, 86.4% (9/22) had hypertriglyceridemia, 68.2% (15/22) diabetes, 50% (11/22) hepatic steatosis, 41% (9/22) insulin resistance, 41% (9/22) hypercholesterolemia, and 18.2% (4/22) hypertension. Genetic analysis was performed in only 45.4% (10/22) of the patients. *AGPAT2* and *BSCL2* gene mutations were identified in 40% (4/10) and 60% (6/10) of them, respectively.

Conventional Echocardiographic Assessment of the CGL and Control Groups

In CGL group, 32% (7/22) presented left ventricular hypertrophy (LVH), 27.3% (6/22) had increased left atrial volume index (LAVI), 18.2% (4/22) had increased LV end-systolic diameter (LVDS) and 4.5% (1/22) had increased LV end-diastolic diameter (LVDD).

Patients with CGL had increased LAVI (*p* < 0.01) and increased left ventricular mass index (LVMI) compared to the control group (*p* < 0.01). LVEF was normal in all participants. Diastolic function was abnormal in 36.6% (8/22) in CGL group, and normal in the control group. The velocities of E, Es and El waves were significantly lower in the CGL patients ≥18 years of age than the control group (Table 1).

There were few morphological valve abnormalities in CGL patients. Mild mitral valvar regurgitation was detected in 18.2% (4/22) using Doppler color flow imaging in CGL group. Few CGL patients presented mild tricuspid regurgitation (3/22), and mild aortic regurgitation (1/22). All these patients were women and 75% (3/4) were aged <18 years.

Global Longitudinal Strain of the CGL and Control Groups

The 2D-STE detected abnormal GLS in 68.2% (15/22) of CGL patients. The proportion of CGL patients with abnormal GLS according to the age range is shown in Table 2. These alterations were not observed in the control group (*p* < 0.01). Considering the genotype, patients with CGL2 (*BCL2* mutation) presented a higher prevalence of abnormal GLS than CGL1 (*AGPAT2* mutation): 83.3% (5/6) versus 50% (2/4), respectively.

Segmental Longitudinal Strain of CGL Patients and Control Group

Compared to the control group, CGL patients presented impairment in GLS and in LV segmental longitudinal

Table 1 Conventional Echocardiographic of 22 Patients with Congenital Generalized Lipodystrophy (CGL) and 22 Control Subjects According to the Age

Age Group	<18 Years (N=30)			≥18 Years (N=14)		
ECHO	CGL (N=15)	Controls (N=15)	P	CGL (N=7)	Controls (N=7)	P
LAVI, mL/m ²	26.0±7.7	18.2±4.8	<0.01*	27.4±8.4	18.8±4.4	0.04*
LVMI, g/m ² ^{ou2,7}	43.4±13.9	27.3±7.7	<0.01*	96.0±23.3	54.3±10.3	<0.01*
EF, %	70.9±4.5	68.6±4.7	0.33	66.1±5.1	69±4.3	0.34
LVDD, mm/m ²	39.0±11.8	41.1±19.7	0.52	29.3±1.5	26.1±1.5	0.64
LVDS, mm/m ²	23.2±7.2	25.8±12.2	0.26	17.9±1.7	15.6±2.0	0.41
E, ms	1.1±0.2	1.1±0.1	0.87	0.8±0.1	1.0±0.1	0.02*
A, ms	0.5±0.1	0.5±0.1	0.16	0.5±0.1	0.5±0.1	0.84
E/A	1.9±0.5	2.2±0.7	0.12	1.3±0.4	1.8±0.4	0.07
Es, ms	12.3±2.7	14.6±2.7	0.23	9±1.9	14.1±2.9	<0.01*
El, ms	17.0±2.7	18.6±2.7	0.09	13.7±4.3	18±1.0	0.02*
E/E'	7.4±1.9	6.5±1.0	0.16	7.7±2.3	6.1±0.9	0.17

Notes: Data were described as mean and standard deviation. *p<0.05 Mann-Whitney test.

Abbreviations: n, number of participants; ECHO, conventional echocardiogram parameters; LAVI, left atrial volume index; LVMI, left ventricular mass index; EF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; E, PW Doppler of early mitral filling; A, PW Doppler of later mitral filling; E/A, ratio of E to A waves; Es, Tissue Doppler of septal mitral annulus velocity; El, Tissue Doppler of lateral mitral annulus velocity; E', mean Es-El; E/E', E/E' ratio.

Table 2 Prevalence of Abnormal Global Longitudinal Strain (GLS) Among 22 Patients with Congenital Generalized Lipodystrophy (CGL) Categorized by Age, According to Reference Ranges³⁵

Age Group (Years-Old)	CGL/Total Patients with Abnormal GLS (%)
0-1	0/1 (0)
2-9	6/8 (80)
10-13	1/3 (33.3)
14-21	4/5 (80)
>21	4/5 (80)

strain (4C, 3C, and 2C chambers). This difference was not detected in apical segments (Table 3).

Global Longitudinal Strain Compared to Conventional ECHO Parameters and Clinical, Metabolic and Genetic Characteristics of CGL Patients

Among 15 CGL patients with abnormal GLS, 93.3% (14/15) had hypertriglyceridemia, 93.3% (14/15) had low HDL-c, 73.3% (11/15) had diabetes, 53.3% (8/15) had hyperinsulinemia and 46% (7/15) had hypercholesterolemia. Among non-insulinized patients, GLS was impaired in 62.5% (5/8) with insulin resistance. [Supplemental Table 1](#) summarizes the clinical, genetic and metabolic characteristics, conventional ECHO parameters, GLS and the medications used by 22 patients with CGL.

Diabetic CGL patients presented a higher prevalence of abnormal GLS than non-diabetic CGL

patients, 73.3% (11/15) vs 57% (4/7), with a mean GLS of -18.34% and -21.35% in the later (p = 0.009).

Table 3 Segmental Longitudinal and Global Longitudinal Strain Data of 22 Patients with Congenital Generalized Lipodystrophy (CGL) and 22 Control Subjects

Segmental LV	CGL	Control	P
Basal inferior	-17.6±6.2	-21.6±3.0	<0.01*
Basal anterior	-16.5±3.9	-22.2±4.8	<0.01*
Basal septal	-16.5±5.4	-20.7±3.4	<0.01*
Basal lateral	-12.5±7.3	-21.2±4.5	<0.01*
Basal posterior	-7.5±10.8	-19.0±3.7	<0.01*
Basal anteroseptal	-16.0±3.5	-20.6±2.6	<0.01*
Mid lower	-19.4±3.3	-22.5±2.8	<0.01*
Mid anterior	-19.6±4.1	-23.2±3.7	<0.01*
Mid septal	-19.1±3.8	-22.7±3.6	0.02*
Mid lateral	-16.7±2.7	-22.5±4.1	<0.01*
Mid posterior	-16.4±3.3	-20.0±3.5	<0.01*
Mid anteroseptal	-20.5±3.9	-23.1±2.4	0.01*
Apical inferior	-23.5±4.3	-24.1±3.4	0.61
Apical anterior	-23.6±4.4	-23.7±4.4	0.91
Apical septal	-24.4±3.7	-24.1±4.1	0.81
Apical lateral	-23.3±4.4	-22.4±4.5	0.49
Apical posterior	-24.6±5.1	-24.2±3.8	0.92
Apical anteroseptal	-26.0±5.9	-24.3±3.6	0.48
Aplax (A3c)	-19.1±3.2	-21.2±2.3	0.01*
A2c	-19.7±3.3	-22.7±2.3	<0.01*
A4c	-18.7±3.6	-22.2±2.9	<0.01*
GLS	-19.2±2.4	-22.1±1.7	<0.01*

Notes: Data were described as mean and standard deviation. *p<0.05 Mann-Whitney test A.

Abbreviations: Aplax (A3c), apical 3-chamber longitudinal strain; A2c, apical 2-chamber longitudinal strain; A4c, apical 4-chamber longitudinal strain; GLS, global longitudinal strain.

There was a moderate correlation between GLS and insulin levels, A1c, blood glucose and age. An inverse correlation was also noted between leptin levels and GLS in the 22 CGL patients (Table 4).

There was a weak correlation between HOMA-IR and GLS, but only 13 patients were not using exogenous insulin and included in this analysis ($r=0.39$, $p=0.253$).

A moderate correlation was found between GLS and EF ($r=-0.49$, $p=0.02$) but none between age and EF ($r=-0.25$, $p=0.2$). Any correlation among these echocardiographic parameters was observed in the control group.

Discussion

This is the first study to evaluate the heart function and morphology of a large sample of young CGL individuals using 2D-STE. This technique detected a high proportion of CGL patients with abnormal systolic function which was not detected with conventional ECHO.

Using the later we found an increased prevalence of LVH, increased LAVI, LVDS and LVDD, and abnormal diastolic function, but no systolic dysfunction in our CGL patients. A cohort of 44 patients with congenital and acquired generalized lipodystrophy (29 CGL patients) assessed by conventional ECHO showed that 54.4% (24/44) had hypertrophic cardiomyopathy, and 13.6% (6/44) presented characteristics of dilated cardiomyopathy.³⁶ Other cross-sectional study of 22 asymptomatic Brazilian patients with CGL observed the high prevalence of cardiovascular abnormalities also using conventional ECHO-concentric LVH, eccentric LVH and abnormal LV geometry, and diastolic dysfunction.³

Some of our patients presented valvar regurgitation with normal cusps associated with enlarged cardiac chambers suggesting that these abnormalities may be secondary to dilatation of the chambers. Cardiac dilatation but with

normal valve morphology was previously described in an autopsy study of CGL patients.³⁷

Using 2D-STE we detected precocious left ventricular systolic dysfunction in a high proportion of CGL patients with normal systolic function when evaluated by conventional ECHO. The higher sensitivity of 2D-STE allows the detection of early abnormalities, due to the objective and quantitative assessment of global and regional myocardial function in all spatial directions. This imaging analysis through the frame-by-frame tracking of natural acoustic markers (speckles) has been shown clinical utility in several pathological conditions.⁷⁻¹¹

Pathophysiological mechanisms of cardiomyopathy in lipodystrophies are not defined yet.^{3,5,36,37} Metabolic disorders, such as severe insulin resistance, high levels of triglycerides, diabetes mellitus and hypoleptinemia would be possible explanations. Our results support this hypothesis, based on the positive correlation of GLS with A1c, blood glucose and insulin, and the negative correlation with leptin levels.

Insulin resistance has been described as a cause of increased LV mass and heart growth.¹³ Insulin acts on insulin-like growth factor (IGF-1) receptors stimulating the stretching of myocardial fibers, causing changes in mass, diameters and, consequently, ventricular contraction.^{38,39} CGL patients usually present severe and early insulin resistance, as we found in our patients. The weak correlation between HOMA-IR and GLS may be explained due to the small number of non-insulinized patients.

In addition to the effect of insulin on cardiac fibers, high levels of serum triglycerides can lead to its accumulation in the heart, a condition referred to as “cardiac steatosis”.⁴⁰⁻⁴² Hypertriglyceridemia was observed in 86.4% of our patients and in 93.3% of patients with altered GLS. This condition may lead to increased cardiac diameters, mass and volumes and LV dysfunction.^{42,43} Using magnetic resonance imaging Nelson et al showed a three-fold accumulation of triglycerides in the myocardial cells of CGL patients compared to a control group, thus suggesting that cardiac impairment may also be caused by the deposition of triglycerides.²

We also found a direct correlation between lower leptin levels and worse GLS in CGL patients. Leptin appears to influence the metabolism of triglycerides in myocytes. An experimental study demonstrated that leptin, acting at the central level, regulates TG cardiac deposition in adult rats with normal leptin sensitivity, increasing lipolysis and reducing lipogenesis.⁴⁴ Thus, hypoleptinemia could lead

Table 4 Correlation Between Clinical and Metabolic Variables and Global Longitudinal Strain (GLS) in 22 Patients with Congenital Generalized Lipodystrophy

Metabolic Variables	Rho	P
Insulin (mU/mL)	0.69*	0.024*
A1c (%)	0.57*	0.005*
Leptin (ng/mL)	-0.51*	0.005*
Blood glucose (mg/dl)	0.50*	0.018*
Age (years)	0.45	0.03*
Triglycerides (mg/dl)	0.36	0.098
Total cholesterol (mg/dl)	0.35	0.107
HDL-c (mg/dl)	0.31	0.147

Note: * $p<0.05$ Spearman correlation test.

to TG accumulation in myocardial cells and may partially explain the changes in cardiac morphology and ventricular function.

In addition to other metabolic disturbances that affect CGL patients, diabetes mellitus is one of the major risk factors for cardiovascular disorders, increasing the risk of coronary artery disease, cardiac autonomic neuropathy, diabetic cardiomyopathy and heart failure, accounting for 2/3 of deaths in diabetic patients.⁴⁵ Hyperglycemia accentuates oxidative stress and leads to the interstitial collagen deposition, fibrosis and apoptosis, which may result in ventricular systolic and diastolic dysfunction.^{46,47} Asymptomatic patients with metabolic syndrome and type 2 diabetes presented altered longitudinal strain, which might be an early finding of LV remodeling and subclinical cardiovascular disease.^{48,49} Diabetes mellitus was presented in 68.2% (15/22) of our CGL patients, where 73.3% of them presented altered GLS, versus 57% in the group of CGL patients without diabetes.

Diabetes and dyslipidemia are risk factors for atherosclerosis, which also triggers LV systolic and diastolic dysfunction. Postmortem findings in CGL patients including atheromatous plaques with stenosis grade of 20% in left and right coronary arteries were previously described.⁵⁰ Autopsy studies also revealed mild thickening of small intramural coronary arteries in affected patients.⁵¹ A 17-year-old CGL girl with acute myocardial infarction and angiographically normal coronary arteries was reported.¹² Although this study did not directly assess coronary circulation, our patients have several risk factors for early coronary atherosclerosis. Thus, we may speculate that subclinical coronary disease may be involved in these abnormalities detected by 2D-STE.

In our study we found impairment of the longitudinal strain in basal and mid-cavity segments of LV, but not in apical segments in CGL patients compared to the control group. A plausible hypothesis for these findings is the higher amount of longitudinal myocardial fibers in the apical segments, which favors cardiac contraction and the delay of the involvement of this region.⁵² Our findings were similar to described by Phellan et al,⁵³ who showed early impairment of the longitudinal strain of the mid-cavity and basal segments in relation to the apical segments in patients with cardiac amyloidosis, a deposit disease.⁵⁴

We observed a higher prevalence of subclinical systolic dysfunction in CGL2 patients (83.3%) compared to CGL1 (50.0%) using 2D-STE. These findings are in accordance with previous studies that showed a high prevalence of cardiac impairment in CGL2.^{36,55,56} This subtype has more

pronounced metabolic abnormalities than CGL1 due to a more intense loss of functional adipocytes.¹⁹

This is the first study to detect cardiac alterations using 2D-STE in patients with this rare disease. However, the relatively small number of patients and the wide range of age attenuate the strength of our findings. Nevertheless, our series is one of the largest of CGL in Brazil. This is also a cross-sectional study, which carried out at one time point and gives no indication of the time sequence of between exposure and outcome.

Conclusion

The 2D-STE revealed precocious left ventricular systolic dysfunction, even with a normal systolic function when evaluated by conventional ECHO in a young population with CGL. Early exposure to hypoleptinemia and/or insulin resistance even before hyperglycemia must be involved in the myocardial damage in these patients.

Early detection of cardiac abnormalities in young CGL patients using 2D-STE may support a more effective treatment to prevent the high morbidity and mortality usually found in this disorder.

Abbreviations

2C, apical 2-chamber longitudinal strain; 2D-STE, Two-dimensional speckle-tracking echocardiography; 3C, apical 3-chamber longitudinal strain; 4C, apical 4-chamber longitudinal strain; A1c, glycohemoglobin A1c; A, Pulsed-wave Doppler of later mitral filling; AGPAT2, 1-acylglycerol-3-phosphate O-acyltransferase 2; BRAZLIPO, Brazilian Group for the Study of Inherited and Acquired Lipodystrophies; BSA, body surface area; BSCL2, Bernardinelli-Seip congenital lipodystrophy type 2 protein; CGL1, congenital generalized lipodystrophy type 1; CGL2, congenital generalized lipodystrophy type 2; CGL, Congenital generalized lipodystrophy; DTI, pulsed-wave Doppler tissue imaging; E/A, ratio of E to A waves; E, Pulsed-wave Doppler of early mitral filling; E', mean of Tissue Doppler of lateral mitral annulus velocity and Tissue Doppler of septal mitral annulus velocity; ECHO, standard conventional echocardiography; EF, ejection fraction; EI, Tissue Doppler of lateral mitral annulus velocity; Es, Tissue Doppler of septal mitral annulus velocity; GLS, global longitudinal strain; HOMA-IR, homeostasis model assessment of insulin resistance; IGF-1, insulin-like growth factor; LAVI, left atrial volume index; LV, left ventricle; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; LVEF, Left

ventricle ejection fraction; LVH, left ventricular hypertrophy; LVMI, LV mass index; PW, Pulsed-wave Doppler; SPSS, Statistical Package for the Social Sciences; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Ethics Approval and Consent to Participate

This study was performed in accordance with the Declaration of Helsinki and was approved by the University Hospital Walter Cantídio Ethics Committee, Fortaleza, Ceara, Brazil (nº 1.916.387). All the patients and their families gave formal consent to participate in the study by signing the free informed consent form prior to their inclusion.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Prof. Dr. Renan Magalhães Montenegro Junior report grants from Aegerion Pharmaceuticals during the conduct of the study. The authors report no other conflicts of interest in this work.

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