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Cardiac dimensions, intraventricular septum thickness in relation to the estimated glucose disposal rate individuals with long-standing type 1 diabetes: a cross-sectional analysis of the PARADISE T1DM study

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ABSTRACT

Aim. Insulin can stimulate the growth of various cells, including cardiomyocytes, through the insulin-like growth factor (IGF) signaling pathway. Insulin resistance (IR), characterized by elevated circulating insu-

lin levels, complicates long-standing type 1 diabetes mellitus (T1DM). This study investigates whether IR in T1DM is associated with cardiac remodeling.

Material and methods. IR was assessed using the estimated glucose disposal rate (eGDR) in 84 adults with T1DM of at least 5 years. Participants with an eGDR at or below the median value were considered more insulin resistant. Transthoracic echocardiography was used to measure left ventricular end-diastolic diameter (LVEDD), intraventricular septal thickness (IVST), right ventricular end-diastolic diameter (RVEDD), and left atrial diameter (LAD). Participants were divided into two groups based on the median eGDR value. Comparisons between groups were made using the Mann-Whitney test.

Results. The median age of the participants was 40.5 years (range: 34.0–51.0), with a T1DM duration of 21.0 years (range: 15.5–27.0) and eGDR of 7.4 (range: 5.1–9.5). Of the participants, 52 (61.9%) were men. Individuals with lower eGDR had larger cardiac diameters (all in cm): LVEDD (4.5 [4.3–4.8] vs 4.75 [4.5–5]; p = 0.01), LVEDD(2.7 [2.5–2.8] vs 2.8 [2.6–2.9]; p = 0.02), end-systolic LAD (3.5 [3.2–3.7] vs 3.8 [3.5–3.9]; p < 0.01), and thicker IVS (0.9 [0.8–1] vs 1.1 [1–1.18]; p < 0.01).

Conclusions. Individuals with T1DM and lower eGDR values exhibited more pronounced cardiac remodeling, with greater LVEDD, RVEDD, and LAD dilation and increased IVST. These findings suggest that people with T1DM at risk of IR have more commonly adverse cardiac structural changes, though causality remains uncertain.

Introduction

Approximately 10% of people with diabetes have type 1 diabetes mellitus (T1DM), which requires lifelong treatment with exogenous insulin injections [1]. Unfortunately, some individuals with T1DM develop insulin resistance (IR) over time, similar to people with type 2 diabetes mellitus (T2DM) [2].

The pathophysiology of IR in T1DM is multifactorial, with contributing factors including obesity, physical inactivity, exogenous insulin treatment, and smoking [2]. The gold standard for assessing IR in T1DM is the hyperinsulinemic-euglycemic clamp [3]. However, the estimated glucose disposal rate (eGDR) is a less time-consuming indirect marker of insulin sensitivity – highly negatively correlated with IR diagnosed with the hyperinsulinemic-euglycemic clamp [4]. IR, as indicated by lower values of eGDR, is associated with the development of macrovascular complications and increased all-cause mortality in T1DM [5,6].

Cardiovascular disease (CVD) is the leading cause of mortality among individuals with T1DM and T2DM [7]. These people often develop left ventricular hypertrophy, diastolic and, over time, systolic heart failure (HF), atrial fibrillation, and ischemic heart disease [8]. One of the proposed pathomechanisms of diabetic cardiomyopathy in T2DM is IR [9]. Liu et al. demonstrated in a prospective cohort study that lower eGDR is associated with future heart failure events in individuals with T2DM [10].

Less is known about echocardiographic changes associated with IR in T1DM. People with T1DM have significantly higher interventricular septal thickness compared to healthy controls [11]. Body mass index (BMI) has been positively associated with left atrial volume and left ventricular mass in adults with T1DM [12]. However, no data on the relation of cardiac dimensions and wall thickness to IR in T1DM individuals are available.

This study compared cardiac dimensions and wall thickness in T1DM individuals with lower and higher eGDR.

Material and Methods

Recruitment

This is a post-hoc analysis of a cross-sectional study using data from the Poznań Atherosclerosis in Adult Patients with long-term Type 1 Diabetes Mellitus Study (PARADISE T1DM Study). The Bioethical Committee at the Poznan University of Medical Sciences, Poznan, Poland, reviewed and approved the study protocol (67/19). Written informed consent was obtained from all individuals before inclusion in the study. Each participant was assigned a unique code to ensure anonymity and confidentiality of sensitive and clinical data.

The research was conducted in accordance with the Declaration of Helsinki [13].

Participants were enrolled between February 2019 and March 2020. Inclusion criteria were: age between 18–65 years, T1DM confirmed by positive antibodies with at least a 5-year duration. Exclusion criteria included symptomatic heart failure, left ventricular ejection fraction (EF) below 50%, and moderate to severe valvular diseases. Professional athletes were also excluded. More details on the study protocol, clinical examinations, and measurements can be found in our previous reports [14–16].

For this analysis, we selected data from baseline anthropometric and clinical evaluations, including standard biochemical workups such as lipid profile, thyroid-stimulating hormone, creatinine, transaminases, C-reactive protein, Albumin to Creatinine Ratio (ACR), and HbA1c. Low-density lipoprotein cholesterol (LDL-C) concentration was estimated using the Friedewald formula [15].

IR Assessment by eGDR

The eGDR highly correlates with the results of the euglycemic-hyperinsulinemic clamp, the gold standard for IR assessment in T1DM. The eGDR was derived from the following formula:

$$\text{eGDR [mg/kg/min]} = 24.31 - (12.22 \times \text{WHR}) - (3.29 \times \text{arterial hypertension}) - (0.57 \times \text{HbA1c})$$

where WHR is the waist-to-hip ratio, arterial hypertension is coded as 1 if present and 0 if not, and HbA1c is glycated hemoglobin [%] [4]. Individuals with an eGDR at or below the median value were considered to be less insulin-sensitive.

Transthoracic Echocardiography (TTE)

Resting TTE was performed by a cardiologist using a 3.5-MHz transducer (3Sc-RS phased array ultrasound probe) on a Vivid S6 echocardiography machine from General Electric Healthcare Technologies. Left ventricular end-diastolic diameter (LVEDD), right ventricular end-diastolic diameter (RVEDD), left atrium diameter (LAD) at the end of systole, and intraventricular septum thickness (IVST) at the end of diastole were assessed in the left parasternal long-axis view according to the Guidelines of the Working Group on Echocardiography of the Polish Cardiac Society and the Consensus Document of the European Association of Cardiovascular Imaging [17,18]. Left ventricular EF was measured from the two- and four-chamber apical views using the biplane Simpson's method.

Data Analysis

The normality of data distribution was tested using Q-Q plots and the D'Agostino-Pearson test [19]. As most data did not follow a normal distribution in eGDR subgroups, summaries are presented as medians and interquartile ranges (IQR). Comparisons between eGDR groups were made using the Mann-Whitney test for unpaired data. Categorical data are presented as numbers (percentages), while numerical data are presented as medians (lower to upper quartiles) and compared using the Fisher exact test. All tests were two-sided, and the p-value was set at < 0.05 as statistically significant. All statistical analyses were made with the custom code of the R-programming language (version 3.6.1.; Vienna, R Project).

We performed a logistic regression analysis to identify factors associated with cardiac remodeling. The dependent variable was defined as increased IVST (>1 cm) [20]. The multivariable model included age, sex (coded as 1 for men), and BMI—well-established factors related to cardiac size—along with the presence of higher IR risk (defined as eGDR at or below the median value) [21].

Results

Comparison of clinical characteristics

The clinical characteristics of both groups are presented in **Table 1**. We investigated 84 adults with a median age of 40.5 (34.0–51.0) years and a diabetes duration of 21.0 (15.5–27.0) years. Fifty-two (61.9%) of them were men. Median eGDR was 7.4 (5.1–9.5). Most participants with eGDR at or below the median value had hypertension and more commonly presented with diabetic retinopathy and kidney disease. They also required metformin, statins, beta-blockers, and ACEI/ARB more frequently but were less often on insulin pumps. These individuals were older (median age difference of 4.5 years), although the duration of T1DM was comparable between both groups. Their cardiometabolic and renal profiles were

worse, with higher systolic and diastolic blood pressure (SBP, DBP), BMI, WHR, HbA1c, white blood cell count (WBC), triglycerides (TGA), and poorer kidney function.

Comparison of Cardiac Remodeling

Table 2 summarizes the echocardiographic findings. People with eGDR below or equal to the median had significantly more dilated end-di-

Table 1. Comparison of clinical characteristics between individuals with T1DM and eGDR > (IR less probable) or ≤ the median (IR more probable).

Clinical feature or parameter	eGDR > the median median (IQR) n = 42 (50%)	eGDR ≤ the median median (IQR) n = 42 (50%)	p-value
	Categorical data N (% of a group)		
Men	23 (54.8)	29 (69.0)	0.18
Current smoker	6 (14.3)	9 (21.4)	0.39
Hypertension	**1 (2.4)**	**38 (90.5)**	**<0.01**
Peripheral diabetic neuropathy	7 (16.7)	12 (28.6)	0.19
Diabetic retinopathy	**9 (21.4)**	**24 (57.1)**	**<0.01**
Diabetic kidney disease	**2 (4.8)**	**10 (23.8)**	**0.01**
Diabetic foot	1 (2.4)	2 (4.8)	0.56
On insulin pump	**12 (28.6)**	**2 (4.8)**	**<0.01**
Metformin	**4 (9.5)**	**12 (28.6)**	**0.02**
Statin	**3 (7.1)**	**11 (26.2)**	**0.01**
Beta-blocker	**2 (4.8)**	**12 (28.6)**	**<0.01**
ACEI/ARB	**2 (4.8)**	**28 (66.7)**	**<0.01**
	Continuous data median (IQR)		
Age [years]	**38.5 (31–51)**	**43 (38–51)**	**0.01**
T1DM duration [years]	19.5 (15–26)	22.5 (17–28)	0.39
SBP [mmHg]	**127 (117.5–136)**	**130 (125–142)**	**0.01**
DBP [mmHg]	**79.5 (75–86)**	**84.5 (77.5–92)**	**0.04**
WHR	**0.8 (0.8–0.9)**	**0.9 (0.9–1)**	**<0.01**
BMI [kg/m^2]	**25.2 (23.5–27.5)**	**28.2 (24.7–31.8)**	**0.01**
HbA1c [%]	**7.4 (7–8.8)**	**8.1 (7.4–9.2)**	**0.01**
White Blood Cells [G/l]	**6.24 (5.22–7.01)**	**7 (6.24–8.03)**	**0.01**
Red Blood Cells [T/l]	4.94 (4.59–5.18)	4.82 (4.68–5.18)	0.86
Hemoglobin [g/l]	14.4 (13.6–15.1)	14.75 (13.6–15.3)	0.8
Sodium [mmol/l]	139 (138–141)	139 (138–140)	0.91
Potassium [mmol/l]	4.15 (4–4.31)	4.31 (4.05–4.65)	0.07
Total cholesterol [mg/dl]	185.5 (171–202)	190 (165–233)	0.5
LDL-C [mg/dl]	100.5 (86–122)	103 (82–132)	0.63
HDL-C [mg/dl]	63.5 (54–71)	55.5 (50–72)	0.15
TGA [mg/dl]	**85.5 (59–102)**	**108.5 (89–150)**	**<0.01**
Non-HDL-C [mg/dl]	119.5 (106–144)	134 (100–159)	0.27
TGA/HDL	**1.30 (0.84–1.85)**	**1.92 (1.08–2.88)**	**<0.01**
ALT [UI/l]	17 (13–20)	18 (14–32)	0.16
AST [UI/l]	18 (16–21)	18.5 (16–27)	0.16
Creatinine [mg/dl]	**0.83 (0.75–0.91)**	**0.91 (0.78–1)**	**0.03**
eGFR [ml/min/1.73m^2]	**104.3 (90–113. 8)**	**92.2 (87.6–103.9)**	**0.01**
ACR [mg/g]	**4 (3–6)**	**6 (3–20.76)**	**0.04**
CRP [mg/l]	1.05 (0.77–1.82)	1.38 (0.73–2.22)	0.2
TSH [µIU/ml]	2.01 (1.15–2.73)	1.68 (1.18–2.3)	0.23

ACR – Albumin to Creatinine Ratio. ALT – Alanine Transaminase. AST – Aspartate Transaminase. BMI – Body Mass Index. HbA1c – Glycated Hemoglobin. HDL-C – High-Density Lipoprotein cholesterol. LDL-C – Low-Density Lipoprotein cholesterol. WHR – Waist-to-Hip Ratio. MCHC – Mean Corpuscular Hemoglobin Concentration. TGA – triglycerides. TSH – Thyroid-stimulating Hormone. eGDR - Estimated Glucose Disposal Rate. SD - Standard Deviation. eGFR - estimated glomerular filtration rate. SBP - Systolic Blood Pressure. DBP - Diastolic Blood Pressure, ACEI angiotensin-converting enzyme inhibitors, ARB - AT1 receptor blockers; p < 0.05 bolded.

Table 2. Comparison of echocardiographic measurements between individuals with T1DM and eGDR > (IR less probable) or ≤ the median (IR more probable).

Echocardiographic measurement	eGDR > the median median (IQR) n = 42 (50%)	eGDR ≤ the median median (IQR) n = 42 (50%)	p-value
LVEDD [cm]	**4.5 (4.3–4.8)**	**4.75 (4.5–5)**	**0.01**
RVEDD [cm]	**2.7 (2.5–2.8)**	**2.8 (2.6–2.9)**	**0.02**
IVST [cm]	**0.9 (0.8–1)**	**1.1 (1–1.18)**	**<0.01**
LAD [cm]	**3.5 (3.2–3.7)**	**3.8 (3.5–3.9)**	**<0.01**
EF [%]	55 (55–60)	55 (55–55)	0.9

LVEDD – left ventricular end-diastolic diameter. LAD – left atrial diamater. RVEDD – right ventricular end-diastolic diameter, EF- ejection fraction, IVST - interventricular septal thickness; p < 0.05 bolded.

Table 3. Multivariable logistic regression model for the presence of IVS hypertrophy defined as IVST > 1 cm (codes as 1) vs IVST ≤ to 1 cm (coded as 0).

Variable	OR [95% CI]	p
Age [years]	1.01 [95% CI: 0.96–1.07]	0.65
Sex (man)	**5.22 [95% CI: 1.47–18.46]**	**0.01**
BMI [kg/m^2]	1.09 [95% CI: 0.96–1.23]	0.17
eGDR ≤median	**7.55 [95% CI: 2.24–25.50]**	**<0.01**

CI – Confidence Interval; OR – Odds Ratio; eGDR - estimated Glucose Disposal Rate, IVST - interventricular septal thickness; p < 0.05 bolded.

astolic left ventricle and right ventricle diameters, end-systolic left atrial diameter, and thicker intraventricular septum at the end of diastole. Although statistically significant, the differences between medians were of low clinical significance, ranging from 0.1 cm for RVEDD to 0.25 cm for LVEDD. Notably, left ventricular EF was comparable between both groups.

The multivariable logistic regression model revealed that thicker interventricular septum (IVS) was positively associated with eGDR ≤ median adjusted for BMI, age, and sex (see **Table 3**). Increased IVST was more common in those with eGDR at or below the median value (more insulin resistant) and in men. Therefore, we included separate analyses of cardiac dimensions for the women and men in the supplementary material (**Supplementary Tables 1** and **2**).

In univariable logistic regression analysis, eGDR at or below the median was positively related to LVEDD (OR 3.40 [95% CI: 1.04–11.14]; p = 0.04) and LAD (OR 4.23 [95% CI: 1.33–13.42]; p = 0.01). However, the association between increased LAD and eGDR at or below the median became nonsignificant after adjusting for sex, age, and BMI (p = 0.64). No participants showed LV dilation defined as LVEDD above 5.9 cm in men or 5.2 cm in women [20].

Discussion

Our study demonstrates that increased risk of insulin resistance (IR), assessed through eGDR, is associated with a worse cardiometabolic and renal profile, more diabetic complications, and more complex pharmacological treatment. Individuals with T1DM and a higher probability of IR are usually overweight. They also tend to have more dilated left and right ventricles, left atrium, and IVS hypertrophy. Increased IVST occurred more often in less insulin-sensitive T1DM individuals, regardless of BMI, age, or sex. These findings indicate that people with T1DM and a higher likelihood of IR exhibit at least mild but adverse cardiac remodeling.

The measurements of left ventricular diameters are related to subclinical heart failure [22]. As assessed by HOMA-IR, insulin resistance is associated with subclinical left ventricular dysfunction in the general population [23]. Compared to healthy controls, increased left ventricular diameter, mass, and left atrial volume are commonly observed in individuals with metabolic syndrome [24]. Additionally, left ventricular diameter has been linked to a higher risk of sudden cardiac death, independent of ejection fraction [25]. These findings are consistent with previous research on

T2DM, which also associates IR with heart failure [10,26]. In T2DM, BMI has been positively associated with left ventricular dimensions, and left ventricular diastolic diameter has been identified as a standalone indicator of mortality risk [27,28]. In our study, men exhibited higher odds of IVS hypertrophy. This finding is in agreement with other studies demonstrating that women have lower left ventricular wall thickness than men [29].

Pathophysiology

The impact of IR on cardiac hypertrophy in T1DM remains less explored, though mechanisms in T2DM provide some insight. Chronic hyperinsulinemia, a hallmark of IR, contributes to increased left ventricular diameters in T2DM [30]. IR impairs the PI3K/Akt signaling pathway, which normally promotes vasodilation and reduces vascular resistance, while leaving the MAPK pathway, which drives cell proliferation and endothelin-1 secretion, largely intact [31,32]. Increased endothelin-1 concentration and sympathetic tone lead to hypertension and cardiac hypertrophy [33]. Over time, the proliferative effects of insulin on vascular smooth muscle cells cause an increase in left ventricular mass and concentric remodeling, potentially going unnoticed until more severe cardiovascular issues arise [30,34]. In people with cardiac hypertrophy due to aortic stenosis, myocardial glucose uptake was lower during high insulin conditions, indicating insulin resistance. This resistance is associated with changes in glucose transporters, specifically a decreased GLUT-4/GLUT-1 ratio [35].

In our study, WBC count was higher in participants with a higher probability of IR and mild, although adverse, cardiac remodeling. This finding aligns with previous research, such as Shi et al., which found a positive relationship between WBC count and left ventricular mass index in hypertensives [36]. Leukocytes play a significant role in diabetic cardiomyopathy in T2DM, with disturbances in metabolic and inflammatory pathways due to pro-inflammatory cytokines, glucose metabolites, and reactive oxygen species during hyperglycemia. This increases leukocyte activation and cardiac inflammation, with neutrophils and macrophages contributing to sustained inflammation and fibrosis [37]. However, whether WBC contributes to cardiac remodeling in people with T1DM is uncertain; a more common finding and potential correlation do not necessarily translate into causation.

Few studies have investigated echocardiographic changes in diabetic cardiomyopathy in T1DM. Weber et al. reported that young adults with T1DM had significantly higher interventricular septal thickness and reduced diastolic parameters than non-diabetic controls [11]. Additionally, echocardiographic parameters such as left ventricular EF <45%, impaired global longitudinal strain, and diastolic mitral early velocity (E)/early diastolic tissue Doppler velocity (e') were predictive of major adverse cardiovascular events (MACE) in people with T1DM without heart disease over a 7.5-year follow-up [38]. Lassen et al. suggested that E/e' and global longitudinal strain (GLS) provide better prognostic value in T1DM women than men [39]. In another study, BMI was positively associated with left atrial volume, left ventricular mass, and transmitral Doppler ratio E/A in T1DM individuals without previous heart disease or hypertension [12]. In a cohort of 20,985 people with T1DM, the incidence of HF was positively associated with HbA1c, age, diabetes duration, BMI, smoking, SBP, and negatively with HDL-C [40]. However, Hjortkjær et al. found that long-term T1DM was associated with smaller left ventricular mass and volumes [41].

Insulin resistance is a well-known risk factor for heart failure and death in people with T2DM [42]. In T1DM individuals with IR, there is also some evidence of worse cardiovascular outcomes. An analysis of women with T1DM aged 65 to 74 showed that the presence of IR was accompanied by a more common history of myocardial infarction [43].

Study Limitations

There are several limitations to this study. First, instead of using the complicated and time-consuming hyperinsulinemic-euglycemic clamp method, we used the indirect eGDR method. However, this approach is increasingly common in daily clinical settings. Another limitation is the cross-sectional nature of the study, which shows that some findings coexist and may be associated but do not establish causation. A prospective

study with long-term follow-up, more detailed cardiovascular evaluation, insulin resistance measurements or animal models might provide clearer answers.

Additionally, this is a single-center study performed on a group of T1DM patients under the constant care of a regional reference center for diabetes. Although the median duration of T1DM was 15 years, these people generally had well-preserved kidney function, lipid profiles, and SBP within target ranges. At least half of them had normal BMI. Even if cardiac remodeling was present, it was mild. In other settings, people with T1DM of similar duration might be in more severe clinical conditions. Although insulin pump treatment is the gold standard in T1DM, it is still not used by all individuals, even in our group. The mode of insulin treatment might also impact the rate of IR, clinical profile, and cardiac remodeling. Finally, the medium sample size and single-center nature of the study may limit the generalizability of our findings.

Future research should aim to include larger and more diverse populations, control groups, comprehensive cardiac assessments, and use gold-standard methods for insulin resistance evaluation to enhance the validity and applicability of the findings.

Perspectives

Among adults with T1DM, increased risk of IR, as estimated by eGDR, is positively associated with adverse cardiac remodeling. It remains unclear whether insulin itself promotes IVS hypertrophy or if other factors contributing to IR are responsible for the adverse cardiac remodeling.

These findings highlight the importance of early identification and management of insulin resistance in T1DM to mitigate cardiac complications potentially. Future studies should focus on longitudinal assessments to better understand the progression of cardiac remodeling in this population and explore targeted interventions to improve cardiovascular outcomes.

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Authors contribution

Michal Kulecki wrote the main manuscript text. He was also responsible for the study's conceptualization, methodology, formal analysis, investigation, and methodology. Dariusz Naskret was responsible for project administration, conceptualization, investigation, and Resources. Mikolaj Kaminski was responsible for formal analysis, supervision, investigation, and resources. Dominika Kasprzak was responsible for conceptualization, investigation, and resources. Pawel Lachowski, Daria Klause, Maria Kozlowska, and Justyna Flotynska were responsible for the investigation and resources. Dariusz Naskret, Aleksandra Uruska, and Dorota Zozulinska-Ziolkiewicz supervised the project. All authors reviewed the manuscript.

Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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Conflict of interest statement

The authors declare no conflict of interest.

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Supplementary Table 1. Comparison of echocardiographic measurements between clinical characteristics between men with T1DM and eGDR > or ≤ the median.

Echocardiographic measurement	eGDR > the median median (IQR)	eGDR ≤ the median median (IQR)	p-value
LVEDD [cm]	**4.7 (4.5–4.9)**	**5.0 (4.8–5)**	**0.01**
RVEDD [cm]	2.7 (2.6–2.9)	2.8 (2.7–2.9)	0.33
IVST [cm]	**1.0 (0.9–1)**	**1.1 (1.1–1.2)**	**<0.01**
LAD [cm]	**3.6 (3.4–3.8)**	**3.9 (3.8–4.0)**	**<0.01**
EF [%]	55 (55–60)	55 (55–55)	0.50

LVEDD – left ventricular end-diastolic diameter. LAD – left atrial diamater. RVEDD – right ventricular end-diastolic diameter, EF- ejection fraction, IVST - interventricular septal thickness; p < 0.05 bolded.

Supplementary table 2. Comparison of echocardiographic measurements between clinical characteristics between women with T1DM and eGDR > or ≤ the median

Echocardiographic measurement	eGDR > the median median (IQR)	eGDR ≤ the median median (IQR)	p-value
LVEDD [cm]	4.3 (4.2–4.5)	4.5 (4.2–4.6)	0.62
RVEDD [cm]	2.6 (2.5–2.7)	2.7 (2.6–3.2)	0.07
IVST [cm]	0.9 (0.8–0.9)	1.0 (0.8–1.1)	0.21
LAD [cm]	3.2 (3.0–3.6)	3.5 (3.1–3.7)	0.27
EF [%]	55 (55–60)	55 (55–55)	0.93

LVEDD – left ventricular end-diastolic diameter. LAD – left atrial diamater. RVEDD – right ventricular end-diastolic diameter, EF- ejection fraction, IVST - interventricular septal thickness.