Changes in Left Ventricular Strain Parameters After Empagliflozin Treatment in Patients with Diabetes Mellitus and Normal Ejection Fraction

Ferhat Işık (frht_0316@hotmail.com)
Diyarbakır Gazi Yaşargil Training and Research Hospital https://orcid.org/0000-0002-1438-3327
Burhan Aslan
Diyarbakir Gazi Yasargil Egitim ve Arastirma Hastanesi
Önder Bilge
Diyarbakır Gazi Yaşargil Training and Research Hospital
Ümit İnci
Diyarbakır Gazi Yaşargil Training and Research Hospital
Ercan Taştan
Diyarbakir Gazi Yasargil Egitim ve Arastirma Hastanesi
Medet Akçay
Diyarbakir Gazi Yasargil Egitim ve Arastirma Hastanesi
Halil Yıldız
Diyarbakir Gazi Yasargil Egitim ve Arastirma Hastanesi
Muhammed Demir
Dicle Universitesi Tip Fakultesi
Mehmet Özbek
Dicle University: Dicle Universitesi
Halil Akın
Ankara Batıkent Medical Park Hospital
Eşref Araç
Diyarbakır Gazi Yaşargil Training and Research Hospital

Research Article

Keywords: Empagliflozin, Diabetes mellitus, Strain

Posted Date: October 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-986178/v1

Abstract

Objective: In recent years, sodium-glucose cotransporter-2 (SGLT-2) inhibitors are known to improve symptoms and reduce mortality in patients with heart failure (HF). Empagliflozin is an antidiabetic drug that SGLT-2 inhibitor. Empagliflozin has beneficial cardiac effects like other SGLT-2 inhibitors. However, data on how empagliflozin treatment affects echocardiographic parameters are limited. We aim to evaluate the changes in left ventricular myocardial strain parameters with 2-dimensional speckle tracking echocardiography (2D-STE) in patients with diabetes mellitus and normal ejection fraction after empagliflozin treatment.

Material and Method: A total of 48 patients were included in our study. The left ventricular ejection fraction (LVEF) of the patients were normal and there were no HF symptoms and findings. Demographic, clinical, and echocardiographic parameters of study population were evaluated. Empagliflozin 10 mg once daily was given to all patients. Initial and at the end of 3rd month, the 2D-STE parameters of all patients were examined.

Results: The median age of the study population was 55.0 (45.0 – 62.5, IQR) years and 27 (56.3 %) of them were female. There was a significant increase in the left ventricle global longutidunal strain (LV-GLS) and left ventricle global circumferential strain (LV-GCS) compared to baseline [respectively; -19.7(-17.5;-20.9) vs -19.2(-17.6;-20.2), p= 0.016 and -18.9(-16.0;-20.8) vs -17.1(-15.8;-18.7), p= 0.003]. Although left ventricular global radial strain (LV-GRS) was increased compared to baseline, it was not significant [37.0(31.0-41.6) vs 36.3(32.4-40.3), p= 0.776].

Conclusion: In our study, left ventricular myocardial strain parameters such as LV-GLS and LV-GCS were improved in diabetic patients with normal ejection fraction after empagliflozin treatment.

Introduction

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a new class of oral anti-hyperglycemic drugs that increase urinary glucose excretion by decreasing glucose reabsorption in the renal proximal tubules [1]. As well as antidiabetic features, its positive cardiac effects are also known. Large randomized and placebo-controlled studies in patients with diabetes who are at high cardiovascular risk have shown that SGLT-2 inhibitors reduce heart failure (HF) hospitalizations within months after treatment [2, 3]. Although many hypotheses have been proposed, the basic mechanisms by which SGLT-2 inhibitors reduce the risk of HF in people with diabetes are not yet fully understood. Considering the reduction in hospitalization because of HF, it may be assumed that the benefits of SGLT-2 inhibitors are due to the positive hemodynamic and metabolic effects on left ventricle (LV) function [4].

Empagliflozin is an SGLT-2 inhibitor. Studies with empagliflozin have been observed similar renal and/or extrarenal benefits as other SGLT-2 inhibitors. Recently, SGLT-2 inhibitors have been shown to reduce cardiovascular death and hospitalizations in patients with systolic and/or diastolic heart failure, with or without diabetes [5]. Although studies are showing the cardiac benefits of empagliflozin, there is no study

in the literature with advanced echocardiographic evaluation such as 2-dimensional speckle tracking echocardiography (2D-STE) in diabetic patients with preserved ejection fraction (EF). In this study, we aim to examine the effect of empagliflozin on LV myocardial strain parameters before and after 3 months of treatment in patients with type-2 diabetes and normal LVEF.

Material And Methods

Our study was designed as a prospective, single-center, and observational study. Fifty-nine patients with known type-2 diabetes mellitus who were followed up in Diyarbakır Gazi Yaşargil Training and Research Hospital Internal Medicine and Endocrinology outpatient clinics between September 1, 2019 - January 31, 2020, were included in this study. All of these patients had an LVEF of more than 50% and had no symptoms or signs of HF. Exclusion criteria other than HF were atrial fibrillation, chronic renal failure, patients with pacemakers, history of moderate to severe valvular disease, presence of active infection, and pregnancy. Empagliflozin 10 mg daily was given to the 52 patients who remained after the exclusion criteria. Before starting empagliflozin, the patients' routine biochemical tests and glycosylated hemoglobin (HbA1c) levels were checked. Body mass index (BMI) and body surface area (BMA) were calculated. 12-lead surface electrocardiography and 2D-STE images were examined. All procedures were repeated at the end of the 3rd month. Four patients who could not tolerate the drug were excluded from the study during follow-up. At the end of the 3rd month, the clinical, laboratory, and echocardiographic assessments of the patients at initial and after treatment were compared. Strain analysis by 2D-STE was performed by two independent of each other experienced cardiologists according to guidelines from 2D grayscale images recorded using EchoPAC software [6].

Echocardiographic Assessment

Vivid S70 systems (GE Healthcare, Horton, Norway) were used to obtain all echocardiographic images, which were then moved to the EchoPAC workstation. Three consecutive cardiac cycles were taken and images acquired at a frame rate of 60-80 frames/sec. Conventional apical 4-chamber, apical 2-chamber, parasternal long-axis, and parasternal short-axis images were obtained for left ventricle and left atrium measurements, wall thickness, systolic and diastolic parameters. Pulse wave doppler velocity measurements were used for LV diastolic parameters. Biplane LVEF was measured by using the modified Simpson method. Analyzes were performed for 3-apical (LV 4-chamber, 2-chamber, and 3-chamber view) and 3 short-axis views (LV basal, mid and apical views). The program tracked LV myocardium's boundaries automatically, with manual adjustments made as required. The program measured strain values in each view after manual adjustments. Aortic valve closure in the apical long-axis view was defined as end systole. After processing all 3 apical views, a 17-segment bull's-eye view was created. Left ventricular global longitudinal strain-transmural, endocardial and epicardial measurements (LVGLS-trans, LVGLS-endo, and LVGLS-epi, respectively) were automatically calculated by the EchoPAC software. The average strain values for global circumferential strain (GCS) and global radial strain (GRS) were obtained

taking apical, mid-ventricular, and basal short-axis parasternal views [6]. Initial and post-treatment strain images of the same patient are shown in Fig. 1.

Statistics

The histogram and Shapiro-Wilks test were used to confirm the normal or non-normal distribution of data. Median value and interquartile range (IQR) (25-75 %) were used in the distribution of parametric variables. The categorical variables were expressed as percentages. Wilcoxon test was used to compare continuous variables. The statistical significance level of the obtained data was interpreted with the “p” value. Values of $p < 0.05$ were considered to be statistically significant. The analysis of the data was performed using SPSS (Statistical Package for Social Science for Windows)-24 packaged software.

Results

Forty-eight patients were included in the study. The median age of the study population was 55.0 (45.0 – 62.5, IQR) years and 27 (56.3 %) of them were female. Almost all of the patients were using metformin (93.7 %) and more than half were using insulin (52 %). Clinical, demographic characteristics, and medications of all patients were given in Table 1. Systolic blood pressure ($p = 0.001$), diastolic blood pressure ($p = 0.012$), BMI ($p < 0.001$), BSA ($p < 0.001$), alanine transaminase ($p= 0.029$), glucose ($p< 0.001$), HbA1c ($p < 0.001$), and triglyceride ($p = 0.001$) were significantly lower after empagliflozin treatment compared to baseline. Hematocrit ($p = 0.001$) and high density lipoprotein ($p = 0.001$) were significantly increase after treatment. Clinical and laboratory parameters of all patients initial and after treatment were given in Table 2.

Table 1
Clinical, demographic characteristics, and medications of all patients

	n	%
Sex	27	56.3
Female	21	43.7
Male		
Hypertension	23	47.9
Hyperlipidemia	13	27.0
Coronary artery disease	12	25.0
Beta blocker	6	12.5
Statin-fibrats	13	27.0
Renin-angiotensin-aldosterone inhibitors	20	41.6
Calcium channel blockers	7	14.5
Mineralocorticoid receptor antagonists	2	4.1
Hydrochlorotiazid-indapamide	11	22.9
Insulin	25	52.0
Biguainde (Metformin)	45	93.7
Sulfonylureas	7	14.5
Thiazolidinediones	4	8.3
Dipeptidyl dipeptidase-4 inhibitors	26	54.1
Glucagon-like peptide-1 receptor agonist	2	4.1
Others	3	6.2

Table 2
Clinical and laboratory parameters of the patients initial and after empagliflozin treatment.

	Initial	After treatment	p value
Body mass index, kg/m²	31.5(28.0-37.8)	30.7(26.2-36.0)	<0.001
Body surface area, m²	1.94(1.85-2.07)	1.93(1.80-1.99)	<0.001
Systolic blood pressure, mm/Hg	120(110-129)	115(110-125)	0.001
Diastolic blood pressure, mm/Hg	70(60-80)	70(60-78)	0.012
Aspartate transaminase, IU/L	17.0(15.0-24.7)	17.0(14.0-20.0)	0.116
Alanine transaminase, IU/L	20.0(15.0-28.7)	15.5(12.2-28.0)	0.029
Glucose, mg/dL	182(141-263)	147(114-179)	<0.001
HbA1c, %	9.15(7.05-10.57)	7.65(6.50-8.90)	<0.001
Potassium, meq/L	4.1(3.9-4.4)	4.1(3.9-4.4)	0.346
Creatinine, mg/dL	0.80(0.70-1.00)	0.76(0.70-1.00)	0.135
Hematocrit	45.4(44.0-48.9)	46.0(44.0-50.0)	0.001
Total colesterol, mmol/L	196(157-227)	202(166-217)	0.337
High density lipoprotein, mmol/L	38(35-41)	40(37-50)	0.001
Low density lipoprotein, mmol/L	122(98-137)	116(104-137)	0.176
Triglyceride, mmol/L	150(123-242)	124(80-189)	0.001
White blood cell, 10^9/ L	8.45(8.00-9.71)	9.00(7.92-10.42)	0.253
Neutrophil, 10^9/ L	5.00(4.35-6.30)	5.35(4.32-6.55)	0.403
Lymphocyte, 10^9/ L	2.80(2.40-3.20)	2.90(2.22-3.30)	0.674
Platelet, 10^9/ L	251(226-307)	267(219-321)	0.242
Data are expressed as median interquartile range, HbA1c: glycosylated hemoglobin			

In echocardiographic findings; LV systolic diameter [26(25-28) vs 27(25-28) p = 0.028], mitral E wave [0.67(0.54-0.78) vs 0.69(0.61-0.77), p = 0.009] and mitral E/e' [5.44(4.60-7.52) vs 6.33(5.00-9.10), p= 0.005] ratio were less than before treatment. Presystolic wave [0.57(0.51-0.64) vs 0.48(0.42-0.64), p < 0.001] higher than before treatment. Echocardiographic findings of the study population are given in Table 3.

Table 3
Echocardiographic findings of the study population

	Initial	After treatment	p value
Heart rate, beat/min	84(74-91)	84(73-91)	0.522
LVdiastolic diameter, mm	45(43-49)	46(44-48)	0.445
LV systolic diameter, mm	27(25-28)	26(25-28)	0.028
Septum thickness, mm	11(10-12)	11(10-12)	0.248
LV posterior wall thickness, mm	10(9-11)	10(10-11)	0.243
Biplane ejection fraction (%)	64(62-66)	65(62-66)	0.667
LV diastolic volume, ml	86(75-98)	83(75-95)	0.168
LV systolic volume, ml	31(27-35)	31(27-33)	0.156
LV diastolic volume index, ml/m^2	43.37(39.18-47.97)	44.36(40.10-48.42)	0.918
LV systolic volume index, ml/m^2	15.45(13.89-18.38)	15.51(14.87-16.96)	0.909
LV mass, g	174(148-205)	170(158-182)	0.588
LV mass index g/m^2	89.71(77.27-98.29)	87.47(76.51-93.81)	0.498
LA volume, ml	41(35-45)	40(35-44)	0.271
LA volume index, ml/ m^2	20.50(17.27-22.79)	21.13(17.72-24.04)	0.667
Mitrale E wave, cm/sec	0.69(0.61-0.77)	0.67(0.54-0.78)	0.009
Mitrale A wave, cm/sec	0.85(0.73-0.96)	0.78(0.70-0.95)	0.980
Mitral E/ e'	6.33(5.00-9.10)	5.44(4.60-7.52)	0.005
Lateral e wave, cm/sec	0.11(0.08-0.15)	0.12(0.09-0.15)	0.547
Lateral a wave, cm/sec	0.12(0.10-0.14)	0.13(0.11-0.16)	0.112
Lateral Sm, cm/sec	0.09(0.07-0.11)	0.10(0.08-0.11)	0.274
Septal e wave, cm/sec	0.08(0.06-0.11)	0.09(0.06-0.11)	0.343
Septal a wave, cm/sec	0.11(0.10-0.14)	0.12(0.10-0.13)	0.245
Septal Sm, cm/sec	0.08(0.08-0.10)	0.09(0.08-0.10)	0.542

Data are expressed as median interquartile range

IVRT: Isovolumetric relaxation time, LV: Left ventricle, LA: Left atrium, Sm: Peak systolic velocity at myocardial segments

	Initial	After treatment	p value
IVRT, ms	90(81-100)	87(80-97)	0.250
LV presistolic wave, cm/sec	0.48(0.42-0.64)	0.57(0.51-0.64)	<0.001
Data are expressed as median interquartile range			
IVRT: Isovolumetric relaxation time, LV: Left ventricle, LA: Left atrium, Sm: Peak systolic velocity at myocardial segments			

LV-GLS [-19.7(-17.5;-20.9) vs -19.2(-17.6;-20.2), p= 0.016] and LV-GCS [-18.9(-16.0;-20.8) vs -17.1(-15.8;-18.7), p= 0.003] were higher than before treatment. LV-GRS did not change after treatment [37.0(31.0-41.6) vs 36.3(32.4-40.3), p= 0.776] (Fig. 2).

Discussion

Empagliflozin is associated with beneficial cardiac outcomes in patients with HF. In our study, the LV myocardial strain parameters of type-2 diabetic patients with normal LV systolic functions were evaluated by 2D-STE before and after 3 months of empagliflozin. To the best of our knowledge, this is the first study to evaluate LV strain parameters before and after treatment by giving empagliflozin to the same patient group. In this group of patients, LV-GLS and LV-GCS increased after empagliflozin treatment compared to initial.

Although it is antidiabetic, empagliflozin has become popular in the treatment of HF in recent years. The mechanism by which empagliflozin improves cardiac function is not clearly understood [7]. There are some theories that explain the extrarenal cardioprotective effects. Pre-experimental studies suggest that SGLT-2 inhibitors may improve the vascular structural properties, interfering with collagen, elastin, advanced glycation end-products [8]. Furthermore, due to SGLT-2 inhibitors increased ketone bodies have been asserted to facilitate myocardial energetics [9]. Actually, myocardial utilization of beta hydroxybutyrate results in a significant increase in adenosine triphosphate (ATP) production concerning glucose and fatty acid oxidation and improved efficiency in a model of isolated working heart by 25% [10]. Apart from these mechanisms, empagliflozin shows direct myocardial effects as well. Mitocondrial Ca^{+2} in cardiomyocytes is considered one of the main activators of ATP syntesis and antioxidant enzymatic network [11]. High cardiac cytoplasmic Na^{+} and Ca^{+2} concentrations and decreased mitochondrial Ca^{+2} concentration are characteristic factors of heart failure and cardiac death caused by hyperglycemia. In a recent study, it was shown that empagliflozin reduces cardiac cytoplasmic Na^{+} and Ca^{+2} concentrations of cardiomyocytes and increases mitochondrial Ca^{+2} [12]. Finally, the proposal of a novel mechanism of action has suggested the hypothesis that the benefit of SGLT-2's in heart failure may be mediated by the sodium-hydrogen exchanger rather than by the effect on glucose reabsorption [13].

In an animal study with empagliflozin, myocardial infarction was induced in non-diabetic subjects by inflating a percutaneous intracoronary balloon into the left anterior descending coronary artery. Then,

myocardial damage was examined by 3D echocardiography and cardiac magnetic resonance (CMR) imaging. The subjects were given empagliflozin 10 mg/day and placebo for 2 months. EF, longitudinal strain, circumferential strain, and radial strain were found to be increased in the empagliflozin group compared to the control group in postinfarction 3D echocardiography. It has been suggested that empagliflozin ameliorates neurohumoral activation and cardiac injury [14]. In the SUGAR-DM-HF study, patients who have type 2 diabetes or prediabetes and reduced EF were examined. Some of these patients were given empagliflozin for 36 weeks. Initial and after treatment strain parameters were examined by CMR imaging. Left ventricular systolic and diastolic volume indices were decreased in the empagliflozin group. LVEF and LV-GLS were observed similar [15]. In another study, diabetic patients with reduced or normal EF given empagliflozin were followed for 12 months. LV-GLS, LV-GCS, and LV-GRS were significantly increased after empagliflozin compared to baseline [16]. In the EMPA-HEART study, it was investigated whether empagliflozin reduced LV mass in patients with type-2 diabetes and coronary artery disease. CMR was used as the imaging method. After 6 months, a significant decrease in body surface area indexed LV mass was observed [17]. As well as their proven effect in decreasing plasma glucose levels, SGLT-2 inhibitors have been shown to have potential benefits in improving other cardiovascular risk factors such as body weight and blood pressure when being well tolerated [18]. In our study, BMI and BSA decreased after empagliflozin. In addition, systolic and diastolic blood pressures decreased from baseline. Symptomatic hypotension was not observed in any patient and blood pressure was well tolerated in the patients. In a study, it was observed that empagliflozin did not change cardiac index or systemic vascular resistance compared to placebo in patients with type-2 diabetes, but rapidly improved LV filling pressure. Also, LV mass index, left atrial (LA) area, left atrium volume index (LAVI), and LV-GLS were also found to be similar compared to placebo [19]. In our study, LV-GLS and LV-GCS increased after empagliflozin treatment, while LA area, LAVI, LV mass, and LV mass index were similar compared to baseline.

Although patients with normal LV systolic function were included in our study population, most patients had subclinical LV diastolic dysfunction. Subclinical LV diastolic dysfunction is highly prevalent in people with type-2 diabetes [20]. In this study, we found that strain parameters such as LV-GLS and LV-GCS improved after treatment in our study population, but we did not investigate the effect of empagliflozin treatment in patients with type-2 diabetes without LV diastolic dysfunction. We think that clinicians should not disregard this in patients with type-2 diabetes.

Limitations

There are several limitations of our study. First, the sample size is not large enough, but the fact of statistical significance with this number of patients might also be seen as indicative of the magnitude of the empagliflozin effects. Second, the patients with normal LV systolic function were included in our study, but most of them had LV diastolic dysfunction. This may be seen due to comorbidities such as hypertension and coronary artery disease apart from diabetes. We do not know whether the positive echocardiographic findings of empagliflozin are seen in pure diabetic patients without comorbidities. This can give ideas to clinicians for new studies. Third, more than half of our study consisted of obese

patients. Optimal echocardiographic images of these patients are more difficult than in patients with normal weight. In some obese patients, the demarcation of the ventricle and atrium boundaries was repeated several times due to its non-echoic structure. However, we do not think that this is a bias, as echocardiographic analyzes are not performed just by a specialist.

Conclusion

Despite many mechanisms currently available, the impact of SGLT-2 inhibitors on cardiac structure and function remains unclear and should be further clarified through detailed studies. As a result of our study, there were improvements in LV myocardial strain parameters and some LV diastolic parameters of the patients after empagliflozin treatment. These results support that previous studies showing cardioprotective effects of empagliflozin.

Declarations

Conflict of Interest

All authors declare that they have no conflict of interest.

Funding

No funding

Compliance with ethical standards

The ethics committee approval required for our study was obtained from the ethics committee of our hospital.

References

1. - Gallo LA, Wright EM, Vallon V (2015) Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diab Vasc Dis Res 12:78–89. doi:10.1177/1479164114561992
2. - Zinman B, Wanner C, Lachin JM et al (2015) EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes.**N Engl**. J Med 373:2117–2128. doi:10.1056/NEJMoa1504720
3. - Verma S, Mazer CD, Al-Omran M et al (2018) Cardiovascular outcomes and safety of empagliflozin in patients with type 2 diabetes mellitus and peripheral artery disease: a subanalysis of EMPA-REG OUTCOME. Circulation 137:405–407. doi:10.1161/CIRCULATIONAHA.117.032031
4. - Lan NSR, Fegan PG, Yeap BB et al. The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: current evidence and future directions. ESC Heart Fail. 2019 Oct; 6(5): 927–935. doi: 10.1002/ehf2.12505

5. - Anker SD, Butler J, Filippatos G et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Aug 27. doi:10.1056/NEJMoa2107038
6. - Voigt JU, Pedrizzetti G, Lysyansky P et al (2015) Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. J Am Soc Echocardiogr 28:183–193. doi:10.1016/j.echo.2014.11.003
7. - Egea OI, Vacas ES, Yurista SR et al. Unraveling the Molecular Mechanism of Action of Empagliflozin in Heart Failure With Reduced Ejection Fraction With or Without Diabetes. JACC Basic Transl Sci. 2019 Oct 23;4(7):831-840. doi: 10.1016/j.jacbts.2019.07.010
8. - Zimlichman R (2014) Treatment of hypertension and metabolic syndrome: lowering blood pressure is not enough for organ protection, new approach-arterial destiffening. Curr Hypertens Rep 16:479
9. - Mudaliar S, Alloju S, Henry RR (2016) Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG outcome study? A unifying hypothesis. Diabetes Care 39:1115–1122
10. - Sato K, Kashiwaya Y, Keon CA et al (1995) Insulin, ketone bodies, and mitochondrial energy transduction. FASEB J 9:651–658
11. - Kohlhaas M, Liu T, Knopp A et al (2010) Elevated cytosolic Na+ increases mitochondrial formation of reactive oxygen species in failing cardiac myocytes. Circulation 121:1606–1613
12. - Baartscheer A, Schumacher CA, Wust RC et al (2017) Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits. Diabetologia 60:568–573
13. - Packer M, Anker SD, Butler J et al (2017) Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure: Proposal of a Novel Mechanism of Action. JAMA Cardiol. Sep 1;2(9):1025-1029. doi: 10.1001/jamacardio.2017.2275
14. - Santos-Gallego CG, Requena-Ibanez JA, Antonio RS et al (2019) Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. J Am Coll Cardiol. Apr 23;73(15):1931-1944. doi: 10.1016/j.jacc.2019.01.056
15. - MY, Lee M, Brooksbank JM, Wetherall K K et al (2021) Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). Circulation. Feb 9;143(6):516-525. doi: 10.1161/CIRCULATIONAHA.120.052186
16. - Ikonomidis I, Pavlidis G, Thymis J et al (2020) Effects of Glucagon-Like Peptide-1 Receptor Agonists, Sodium-Glucose Cotransporter-2 Inhibitors, and Their Combination on Endothelial Glycocalyx, Arterial Function, and Myocardial Work Index in Patients With Type 2 Diabetes Mellitus After 12-Month Treatment. J Am Heart Assoc. May 5;9(9):e015716. doi: 10.1161/JAHA.119.015716
17. - Verma S, Mazer CD, Yan AT et al. Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease. The EMPA-HEART CardioLink-6 Randomized Clinical Trial. Circulation. 2019 Nov 19;140(21):1693–1702. doi: 10.1161/CIRCULATIONAHA.119.042375

18. - Schwartz SS, Ahmed I. Sodium-glucose cotransporter 2 inhibitors: an evidence-based practice approach to their use in the natural history of type 2 diabetes. Curr Med Res Opin. 2016 May;32(5):907–19. doi: 10.1185/03007995.2016.1151774
19. - Rau M, Thiele K, Hartmann NUK et al. Empagliflozin does not change cardiac index nor systemic vascular resistance but rapidly improves left ventricular filling pressure in patients with type 2 diabetes: a randomized controlled study. Cardiovasc Diabetol. 2021 Jan 7;20(1):6. doi: 10.1186/s12933-020-01175-5
20. - Bouthoorn S, Valstar GB, Gohar A et al (2018) The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: a systematic review and meta-analysis. Diab Vasc Dis Res 15:477–493

Figures

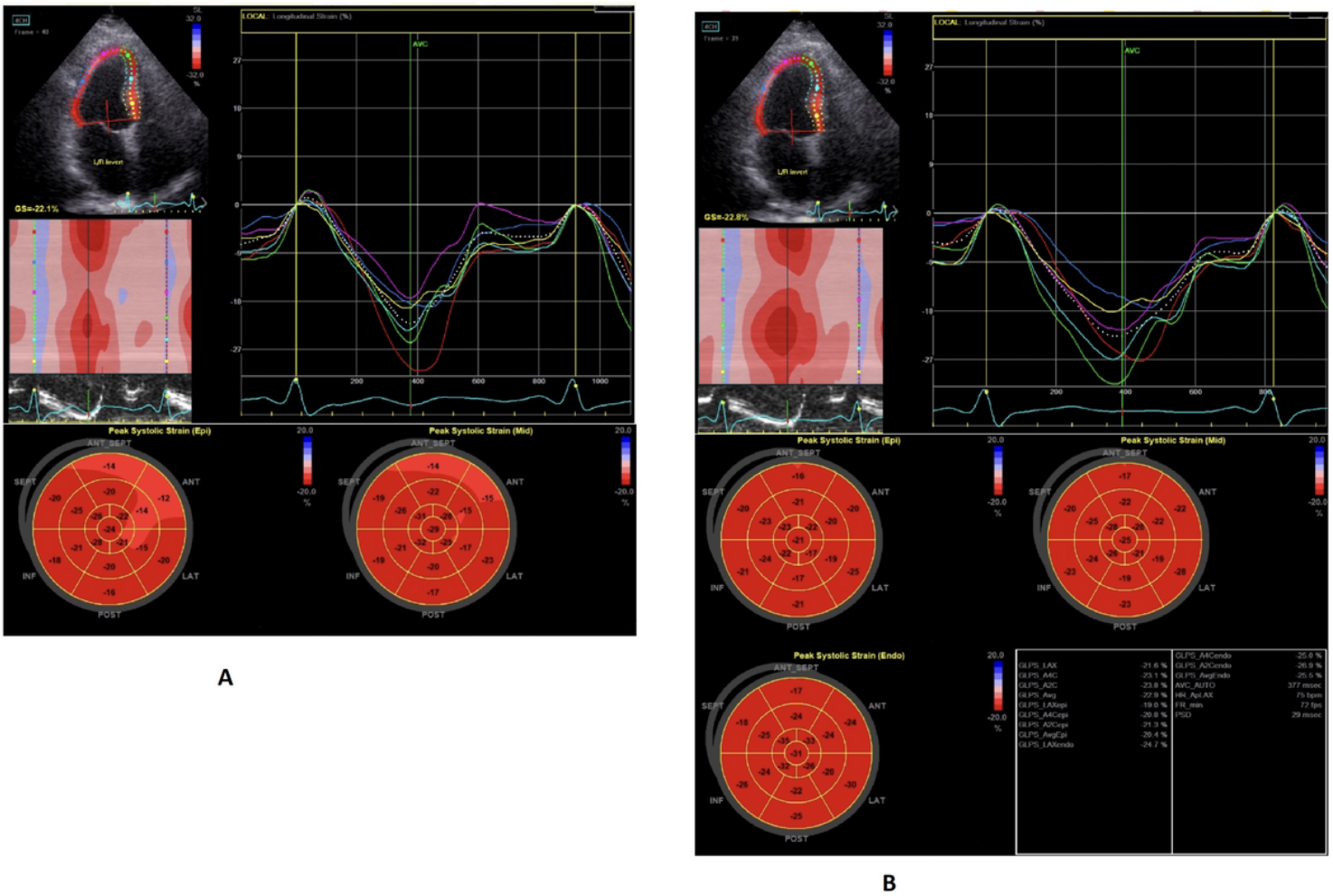
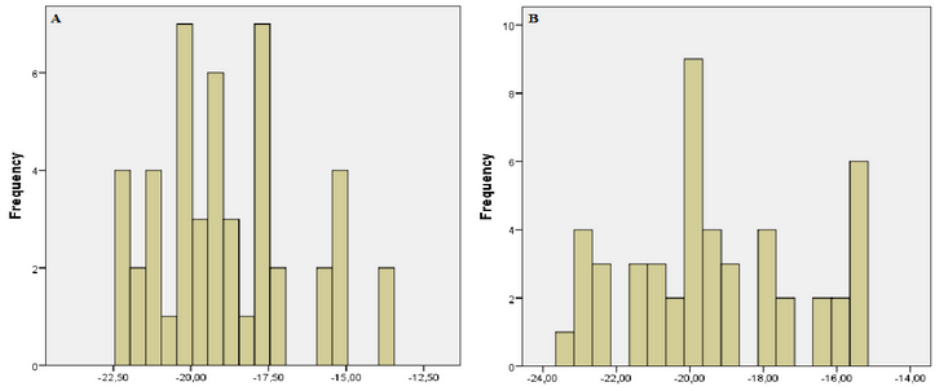
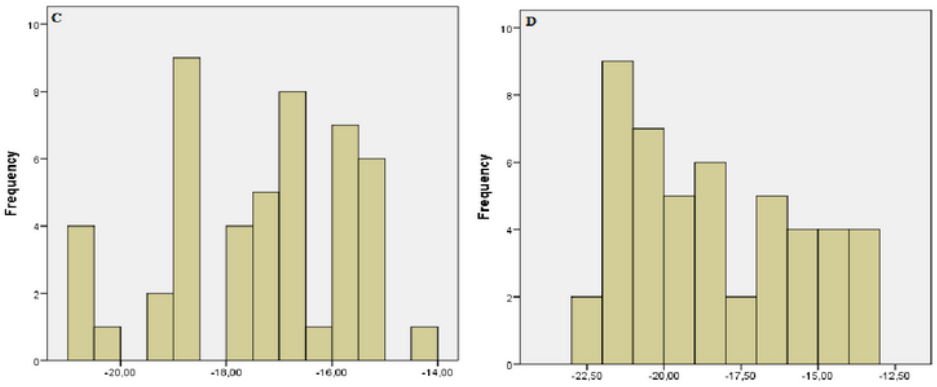


Figure 1

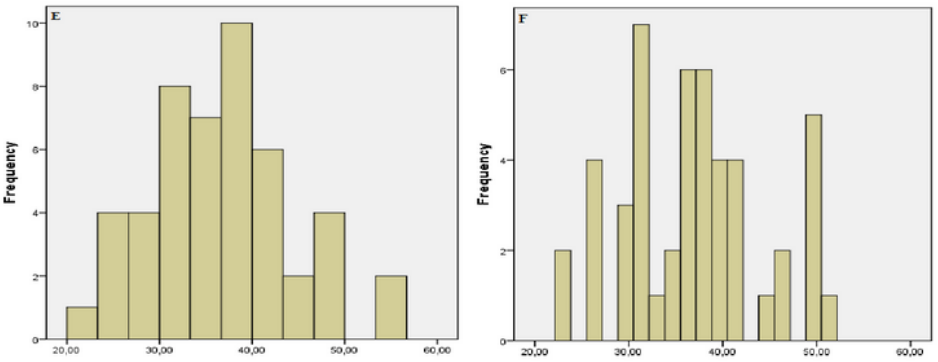
a. A sample of initial 2D-STE analysis of the same patient b. A sample of after empagliflozin treatment 2D-STE analysis of the same patient



A [Initial LV-GLS: -19.2(-17.6;-20.2)] vs **B** [After treatment LV-GLS: -19.7(-17.5;-20.9)], p= 0.016



C [Initial LV-GCS: -17.1(-15.8;-18.7)] vs **D** [After treatment LV-GCS: -18.9(-16.0;-20.8)], p= 0.003



E [Initial LV-GRS: 36.3(32.4-40.3)] vs **F** [After treatment LV-GRS: 37.0(31.0-41.6)], p= 0.776

LV-GLS: Left ventricle global longitudinal strain, LV-GCS: Left ventricle global circumferential strain, LV-GRS: Left ventricle global radial strain

1

Figure 2

Comparison of initial and after empagliflozin treatment in LV myocardial strain parameters