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Effects of Dapagliflozin on Left Atrial Ejection Force in Heart Failure with Preserved Ejection Fraction: DAPA-Left Atrial Ejection Force Trial

ABSTRACT

Background: Left atrial ejection force (LAEF) represents the force exerted by the left atrium (LA) to push blood into the left ventricle (LV) at the end of diastole. It is calculated as LAEF = 1/3 × mitral orifice area × (peak A velocity)^2.

Methods: The primary endpoint was to assess changes in LAEF after 6 months of sodium-glucose co-transporter-2 inhibitor (SGLT-2 inhibitor) therapy in patients with heart failure with preserved ejection fraction (HFpEF). Secondary endpoints include changes in diastolic function, LV global longitudinal strain (LV-GLS), and LA strain parameters.

Results: In this single-center, prospective, randomized open-label study, 100 HFpEF patients were divided into 2 groups (n = 50 each). The study group received Dapagliflozin 10 mg daily along with guideline-directed medical therapy (GDMT) for 6 months, while the control group received only GDMT. The study group showed a significant reduction in LAEF (143.74 ± 10.33 to 134.4 ± 8.82; $P < .001$), LV-GLS improvement (−15.9 ± 4.13 to −17.1 ± 3.53; $P < .001$), and enhanced LA strain parameters (LA reservoir strain: 28.74 ± 9.31% to 36.39 ± 12.3%; LA contractile strain: −12.8 ± 5.41 to −17.89 ± 6.85; LA conduit strain: −15.97 ± 5.49 to −22.5 ± 8.25; all $P < .001$). Additionally, left ventricular mass index (199.9 ± 21.17 to 186.24 ± 16.77; $P < .001$) and left atrial volume index (36.17-32.21 mL/m^2; $P < .001$) significantly decreased.

Conclusion: Dapagliflozin significantly reduces LAEF while improving LA strain and LV-GLS, reinforcing its role in LA and LV reverse remodeling in patients with HFpEF.

Keywords: Left atrial ejection force, atrial strain, sodium-glucose co-transporter-2 inhibitor, heart failure with preserved ejection fraction

ORIGINAL INVESTIGATION

INTRODUCTION

Heart failure (HF) is a global health issue affecting millions worldwide, and heart failure with preserved ejection fraction (HFpEF) constitutes more than half of all HF cases.[1] Treatment of HFpEF traditionally focuses on the management of comorbidities such as diabetes, obesity, hypertension, and atrial fibrillation (AF). Although medications that improve outcomes in heart failure with reduced ejection fraction (HFrEF) have not been consistently shown to benefit HFpEF in terms of reducing all-cause or cardiovascular (CV) mortality, they have been effective in decreasing HF hospitalizations in this population.[2,3] Among these medications, sodium-glucose cotransporter 2 (SGLT-2) inhibitors have demonstrated significant CV and renal benefits irrespective of diabetes status.[4-8]

Studies have shown that SGLT-2 inhibitors can prevent the enlargement of the left atrium (LA) diameter, reduce interstitial fibrosis, and decrease the incidence of AF inducibility in both type 2 diabetes mellitus (T2DM) and non-diabetic patients.[9,10] Recent meta-analyses showed that SGLT-2 inhibitors, particularly dapagliflozin, offer several benefits for patients with HFpEF in the form of reduced risk of hospitalization for HF and CV mortality, lower NT-pro-BNP levels, and improved exercise capacity and quality of life, suggesting that SGLT-2 inhibitors may be a valuable treatment option for HFpEF patients.[11-13] Sodium-glucose cotransporter 2 inhibitors were approved as a therapy for HFpEF as per the 2023 Update of ESC

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Guidelines for the diagnosis and treatment of acute and chronic heart failure and American Heart Association 2022 HF guidelines.[14,15]

Left atrium ejection force (LAEF) has been used as a measure of LA systolic function. It refers to the force exerted by the LA to force blood into the left ventricle (LV) at the end of ventricular diastole. Based on Newton's second law, LAEF is calculated as the product of the mass and acceleration of blood from the LA during atrial systole.[16] It has been previously studied in patients with myocardial infarction, hypertension, hypertrophic cardiomyopathy, and to assess LA function following successful catheter ablation for AF.[17-20] Recently, a study by Hafez et al[16] has shown that LAEF is high in patients with HFpEF and can be used as a measure to diagnose it. There is no study to date that has demonstrated the effect of dapagliflozin on LAEF in patients with HFpEF. Hence, this study aims to evaluate the impact of SGLT-2 inhibitor dapagliflozin on LAEF in patients with HFpEF while simultaneously assessing the changes in LA and LV strain parameters as well.

METHODS

Study Design and Setting

This is a single-center, prospective, randomized open label study (DAPA-LAEF Trial) conducted among patients with an established diagnosis of HFpEF with an age range between 18 years and 80 years with a body mass index (BMI) of <45 kg/m^2, who were diagnosed with HFpEF based on the criteria of HFA-PEFF score (score >4).[21] Patients with chronic HF diagnosed at least 3 months before enrollment and currently in New York Heart Association (NYHA) class II-IV with preserved EF (LVEF) ≥50%, and elevated NT-pro-BNP >125 pg/mL without AF were also included in the study. Patients have been randomized to either the dapagliflozin or guideline-directed medical therapy (GDMT) group using the method of block randomization with a block size of 4 to ensure a balanced allocation of patients to each treatment group. The study was conducted at the Department of Cardiology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research (GIPMER), New Delhi, from March 2023 to July 2024. The study was performed with the approval of the Institutional Ethics Committee on clinical investigation (Approval no. F.1/IEC/MAMC/104/10/2023/no.46). One hundred consecutive patients of HFpEF were included in this study and divided into 2 groups. Patients underwent clinical, biochemical, and echocardiographic evaluation at baseline and then were randomized either to receive dapagliflozin 10 mg once daily in addition to GDMT or to continue GDMT only. After 6 months from randomization, patients underwent a new clinical, biochemical, and echocardiographic evaluation to assess the changes over time. The primary endpoint was to assess change in LAEF after 6 months of dapagliflozin therapy. Secondary endpoints were to see changes in diastolic functions, LV global longitudinal strain (LV-GLS), and LA strain parameters after 6 months in both groups. The secondary endpoint also includes change in NT-ProBNP level and composite events of all-cause mortality or first heart failure hospitalization at the end of 6 months follow-up.

Guideline directed medical therapy includes a combination of an angiotensin-converting enzyme inhibitor or an angiotensin receptor neprilysin inhibitor and a mineralocorticoid receptor antagonist, along with anti-diabetic drugs in diabetic patients. Holter monitoring was done for 48 hours to rule out paroxysmal AF.

Patients having more than mild mitral stenosis/mitral regurgitation/aortic regurgitation/aortic stenosis, LVEF <50%, patients with AF, hypertrophic cardiomyopathy without signs or symptoms of HFpEF, and recent (<1 month) acute coronary syndrome were excluded from the study. Patients with a history of coronary artery bypass graft or valve replacement surgery, recent (<1 month) hospitalization for decompensated HF, contraindicated for SGLT-2 inhibitors and systolic blood pressure <100 mm Hg were also excluded from the present study.

Trans-Thoracic Echocardiography Examination

Standard trans-thoracic ECHO was performed by an experienced echocardiographer using an EPIQ 7 ultrasound scanner (Phillips, the Netherlands) with an X5-1 matrix array probe having a frequency range of 5-1 MHz. The measurements were assessed as per the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[22] Left ventricular mass and systolic functions (LVEF) were measured using the modified biplane Simpson method from the apical 4 and 2-chamber views. The M-mode ECHO was used to measure internal LV end-diastolic diameter (LVEDD), LV posterior wall thickness at end-diastole (PWTD), and interventricular septum thickness at end-diastole (IVSTD), from the parasternal short-axis view at the level of papillary muscles.

LV mass in grams was calculated using the following formula:

LV mass = 0.8 x 1.04 x [(LVEDD + PWTD + IVSTD) 3- (LVEDD) 3]) + 0.6

To calculate LVMI in g/m^2, LV mass was divided by body surface area (BSA).

Relative wall thickness (RWT) was calculated by dividing 2×PWTD by the LVEDD.

Left Atrial Volume and Left Atrial Ejection Force

LA volume was measured using the area-length method from the apical 2- and 4-chamber views at ventricular end systole. This measurement was divided by BSA to obtain LAVI.

HIGHLIGHTS

- Left atrial ejection force is the force exerted by LA to force blood into the LV at the end of diastole.
- First study to evaluate the effects of dapagliflozin on LAEF in HFpEF.
- Dapagliflozin reduces LAEF and improves LA strain and LV-GLS.
- When LA strain isn't available, LAEF helps to diagnose HFpEF.

LAEF was calculated by using the following formula:

LAEF = 1/3× MOA × (peak A velocity)^2 where MOA is the mitral orifice area and A is the velocity of the late diastolic wave of mitral flow (atrial systole).

LAEF in K dynes = 1/3 x mitral valve area (MVA) x (trans-mitral A wave velocity)^2

The MVA was assessed by 2-D planimetry. This was obtained by tracing the narrowest mitral orifice from the parasternal short-axis view, ensuring the trace was tangential to the mitral annulus.

Corrected LAEF for age (% LAEF) was calculated using the formula:

% LAEF = (Calculated LAEF / the normal LAEF according to age) ×100

The normal LAEF according to age was estimated as (0.098 × age) – 0.74

Doppler Imaging

From the apical 4-chamber view, trans-mitral pulsed wave Doppler at the mitral valve leaflet tips was used to estimate peak early diastolic filling (E-wave) and late diastolic filling (A-wave) velocities, as well as the E/A ratio.

Tissue Doppler Imaging

Color-coded tissue Doppler imaging was applied to a gray-scale apical 4-chamber view. Pulsed-wave Doppler was applied to the lateral and medial aspects of the mitral annulus. Lateral and septal e' wave velocities for early diastolic myocardial relaxation were recorded. These velocities were averaged to estimate the mean E/e' ratio. The E/e' ratio was calculated as the index of the LV filling pressure.

Left Atrium Strain

Speckled tracking echocardiography (STE) was performed on Philips EPIQ 7, the Netherlands using S5-1 MHz transducer with one lead electrocardiogram recording providing an angle-free assessment of the atrial deformation. Left atrial strain and strain rate were measured in the apical 4-chamber view with the onset of the QRS complex used as the zero-reference point (R-R gating), according to current guidelines.[22] The mean frame rate was 60 ± 10 frames per second. After placing 3 landmarks, 2 at the mitral annulus and the other at the atrial roof, it traced the endocardium and defined the region of interest (ROI). The LA average strain is the combination of the 3 LA walls (left wall, right wall, and roof). LA strain curves were delivered from that average strain, and the software provided us with the LA strain values, including the LA reservoir strain (peak longitudinal strain), a contractile strain (active atrial contraction) and LA conduit strain (passive atrial emptying). Automatic tracking of the LA wall by the software (auto-strain QLAB 13.0, Philips Medical Systems, Andover, MA, USA) was visually verified and corrected by adjusting the ROI or the width of the contour, ensuring appropriate capture of LA motion. All echocardiograms were independently evaluated by 2 observers and any difference of opinion was settled by mutual consensus.

Left Ventricle Global Longitudinal Strain

Left ventricle global longitudinal strain (LV-GLS) was determined by using the 2D-STE. Three standard apical views [apical 2-chamber (A2C), apical 3-chamber (A3C), and apical 4-chamber (A4C)] were obtained at rest as per the ASE recommendations.[23] The assessment of global longitudinal peak systolic strain was performed offline. Endocardial borders were traced manually. They were visualized as a color-coded sequence in the individual clips and then combined in a bull's-eye plot. For each of the views, well-defined cardiac cycles were acquired and stored for offline analysis using the Auto strain software (QLAB 13.0, Philips Medical Systems, Andover, MA, USA). The software then calculated the regional average of the apical 2-chamber, 4-chamber, and 3-chamber views of the 17 segments at an end-systolic frame.[24] All echocardiograms were independently evaluated by 2 observers and any difference of opinion was settled by mutual consensus.

No artificial intelligence (AI)—assisted technologies [such as large language models (LLMs), chatbots, or image creators] were used in the production of submitted work.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 26 (IBM Inc., Armonk, NY, USA). Descriptive statistics were used to describe categorical variables (frequency and percentages) and continuous variables [mean and standard deviation (SD) or median and range (depending on the normality of data)]. The comparison of the variables which were quantitative and not normally distributed in nature was analyzed using the Mann–Whitney U test, and variables which were quantitative and normally distributed in nature were analysed using the Shapiro-Wilk test. Paired *t*-test/Wilcoxon signed rank test was used for comparison across follow-up. The comparison of the variables that were qualitative in nature was analyzed using the chi-square test. If any cell had an expected value of less than 5, then Fisher's exact test was used. Spearman's rank-order correlation was performed to assess the significance of the correlation between numerical variables. Independent associations of changes in LAEF and LA strain curve parameters between baseline and 6 months after administration of SGLT-2 inhibitor with echocardiographic parameters were evaluated using multiple linear regression analyses. *P*-value < .05 was chosen to indicate the significance of statistical tests.

RESULTS

Fifty patients of HFpEF were included in each group. The majority of patients were women 55 (55%) in the overall group. The mean age of the patients was 47.62 ± 8.91 years, and their average BMI was 32.68 kg/m^2. Baseline and clinical characteristics were similar in both groups. Hypertension was present in 91% of overall patients (Table 1).

Echocardiographic parameters are presented in Tables 2-4. Baseline values for all echocardiographic variables were comparable in both groups (Table 2). Echocardiographic parameters show that the mean LVEF was 62.86 ± 3.70%. The

Table 1. Comparison of Baseline Characteristics between DAPA and Control

Demographic Characteristics	DAPA (n = 50)	Control (n = 50)	P
Gender			0.841†
Female	28 (56%)	27 (54%)	
Male	22 (44%)	23 (46%)	
Smoker	13 (26%)	16 (32%)	0.66†
Hypertension	47 (94%)	44 (88%)	0.486*
Diabetes mellitus	19 (38%)	21 (42%)	0.838†
Left ventricular hypertrophy#	29 (58%)	32 (64%)	0.682†
Age (years)	48.28 ± 8.53	46.96 ± 9.31	0.462‡
BMI (kg/m^2)	32.84 ± 1.46	32.53 ± 2.41	0.448‡
Urea (mg/dL)	27.46 ± 4.32	27.4 ± 4.62	0.947‡
Bilirubin (mg/dL)	0.86 ± 0.11	0.86 ± 0.13	0.852‡
RBS (mg/dL)	91.42 ± 8.56	91.86 ± 9.98	0.813‡
HFA-PEFF score	5 ± 0.36	5 ± 0.42	1‡

BMI, body mass index; RBS, random blood sugar. ‡Independent *t*-test; *Fisher's exact test; †chi square test; #echocardiography criteria.

mean E/A ratio in the overall study group was 1 ± 0.38. The average MVA was 4.74 ± 0.42 cm^2. In the control group, there were no significant statistical changes seen after 6 months in all echo-Doppler parameters (E/A, E/e', LAVI). Meanwhile, study group showed significant changes in most echo-Doppler variables at 6 months of follow-up. The E/A ratio was significantly lower in the study group after dapagliflozin therapy in comparison to control ($P < .001$). Average E/e' ratio was significantly lower in the study group after dapagliflozin therapy; 13.8 ± 3.2 to 10.7 ± 1.4, $P < .001$. Significant changes were noted in LAVI after 6 months of dapagliflozin therapy in the study group (mean difference −3.964(3.34 to 4.588); $P < .001$). LAVI significantly decreased from 36.17 mL/m^2 to 32.21 mL/m^2 following the administration of dapagliflozin ($P < .001$) in the study group, but it was statistically not significant in the control group (Tables 3 and 4).

Left Atrium Ejection Force

Left atrial ejection force (%) was similar in both groups 143.74 ± 10.33 versus 142.76 ± 7.89, respectively (Table 2). Mean change in the LAEF before and after 6 months administration of dapagliflozin was −9.34% [95% confidence interval [−7.444 to −11.236]; $P < .001$] in the study group, whereas change was statistically nonsignificant in the control group (Tables 3 and 4). LAEF % decreased from 143.74 ± 10.33 to 134.4 ± 8.82 in the study group ($P < .001$).

Left Atrium Mass and Systolic Function

Left ventricle ejectionwas normal in both groups. Significant changes were noted in left ventricular mass index (LVMI) after 6 months of dapagliflozin therapy in the study group;

Table 2. Baseline Comparison of Echocardiographic Parameters Between Dapa and Control Before Intervention

Echocardiographic Parameters	DAPA (n = 50)	Control (n = 50)	P
LVEF (%)	63.28 ± 2.86	62.44 ± 4.38	0.259‡
RWT (cm)	0.46 ± 0.05	0.47 ± 0.04	0.160‡
E vel (m/s)	0.71 ± 0.05	0.70 ± 0.05	0.348‡
A vel (m/s)	0.78 ± 0.04	0.79 ± 0.05	0.380‡
E/A	1.01 ± 0.39	0.99 ± 0.37	0.800‡
e' lateral (cm/s)	8.42 ± 0.65	8.57 ± 0.86	0.321‡
e' medial (cm/s)	7.11 ± 0.65	7.06 ± 0.78	0.728‡
E/e'	13.80 ± 3.20	12.96 ± 2.64	0.324‡
MVA(cm^2)	4.76 ± 0.37	4.71 ± 0.46	0.55‡
LAVI (mL/m^2)	36.17 ± 1.28	36.04 ± 2.43	0.747‡
LVMI (kg/m^2)	199.90 ± 21.17	202.80 ± 24.88	0.532‡
LAEF (%)	143.74 ± 10.33	142.76 ± 7.89	0.595‡
LV-GLS (%)	−15.90 ± 4.13	−16.14 ± 4.40	0.774‡
LASr (%)	28.74 ± 9.31	27.50 ± 9.15	0.503‡
LAScd (%)	−15.97 ± 5.49	−16.85 ± 5.50	0.425‡
LASct (%)	−12.80 ± 5.41	−13.88 ± 5.44	0.322‡
NT-proBNP (pg/mL), median (25th–75th percentile)	336 (180.7–514.4)	349.2 (181.9–511.8)	0.907§

LAEF, left atrial ejection force; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RWT, relative wall thickness; LAScd, left atrial strain during conduit phase; LASct, left atrial strain during contraction phase; LASr, left atrial strain during reservoir phase; LV-GLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro B-type natriuretic peptide. ‡Independent t-test, §Mann–Whitney U test.

Table 3. Post-Intervention Echocardiographic Parameters Between DAPA and Control

Echocardiographic Parameters	DAPA (n = 50)	Control (n = 50)	P
LVEF (%)	63.50 ± 2.80	63.10 ± 3.00	.580‡
RWT (cm)	0.45 ± 0.04	0.48 ± 0.05	.180‡
E vel (m/s)	0.67 ± 0.04	0.72 ± 0.05	<.001‡
A vel (m/s)	0.77 ± 0.03	0.81 ± 0.04	.363‡
E/A	0.89 ± 0.08	0.92 ± 0.07	.001‡
e' lateral (cm/s)	8.44 ± 0.66	8.56 ± 0.85	.321‡
e' medial (cm/s)	7.10 ± 0.64	7.07 ± 0.76	.728‡
E/e'	10.7 ± 1.4	11.6 ± 2.6	.034‡
MVA (cm^2)	4.74 ± 0.37	4.71 ± 0.45	.600‡
LAVI (mL/m^2)	32.2 ± 1.73	35.5 ± 2.95	<.001‡
LVMI (kg/m^2)	186.24 ± 16.77	198.62 ± 25.47	<.001‡
LAEF (%)	134.4 ± 8.82	140.14 ± 8.12	<.001‡
LV-GLS (%)	−17.1 ± 3.53	−16.28 ± 3.83	.021‡
LASr (%)	36.39 ± 12.33	27.23 ± 8.97	<.001‡
LAScd (%)	−22.5 ± 8.25	−17.34 ± 5.6	<.001‡
LASct (%)	−17.89 ± 6.85	−13.55 ± 4.89	<.001‡
NT-proBNP (pg/mL), median (25th–75th percentile)	128 (108.5-230)	304.5 (184.5-504.75)	<.001§

LAEF, left atrial ejection force; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAScd, left atrial strain during conduit phase; LASct, left atrial strain during contraction phase; LASr, left atrial strain during reservoir phase; LV-GLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro B-type natriuretic peptide; RWT, relative wall thickness. ‡Independent t-test, §Mann–Whitney U test.

Table 4. Comparison of Parameters between Pre- and Post-Intervention in DAPA Group

Parameters	Pre-Intervention (n = 50)	Post-Intervention (n = 50)	Mean Difference 95% CI	*P*
LVEF (%)	63.28 ± 2.86	63.50 ± 2.80	0.220 (−1.329 to 0.889)	.6992¶
RWT (cm)	0.46 ± 0.05	0.45 ± 0.04	0.010 (−0.008 to 0.028)	.2748¶
E vel (m/s)	0.71 ± 0.05	0.67 ± 0.04	0.040 (0.022 to 0.058)	<.001¶
A vel (m/s)	0.78 ± 0.04	0.77 ± 0.03	0.010 (−0.004 to 0.024)	.1636¶
E/A	1.01 ± 0.39	0.89 ± 0.08	0.120 (0.010 to 0.230)	.0381¶
e′ lateral (cm/sec)	8.42 ± 0.65	8.44 ± 0.66	0.020 (0.277 to 0.237)	.8793¶
e′ medial (cm/sec)	7.11 ± 0.65	7.10 ± 0.64	0.010 (0.243 to 0.263	.9385¶
E/e′	13.8 ± 3.2	10.7 ± 1.4	3.100 (2.132 to 4.068)	<.001¶
MVA (cm^2)	4.76 ± 0.37	4.74 ± 0.37	0.020 (−0.125 to 0.165)	.7881¶
LAVI (mL/m^2)	36.17 ± 1.28	32.2 ± 1.73	3.964 [3.34 to 4.588]	<.001¶
LVMI (kg/m^2)	199.9 ± 21.17	186.24 ± 16.77	13.66 [9.296 to 18.024]	<.001¶
LAEF (%)	143.74 ± 10.33	134.4 ± 8.82	9.34 [7.444 to 11.236]	<.001¶
LV-GLS (%)	−15.9 ± 4.13	−17.1 ± 3.53	1.206 [0.563 to 1.849]	<.001¶
LASr (%)	28.74 ± 9.31	36.39 ± 12.33	−11.656 [−13.909 to −9.403]	<.001¶
LAScd (%)	−15.97 ± 5.49	−22.5 ± 8.25	6.527 [4.85 to 8.204]	<.001¶
LASct (%)	−12.8 ± 5.41	−17.89 ± 6.85	5.097 [3.695 to 6.499]	<.001¶
NT-proBNP (pg/mL), median (25^{th}–75^{th} percentile)	336 (180.7-514.4)	128 (108.5-230)	—	<.001**

LAEF, left atrial ejection force; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAScd, left atrial strain during conduit phase; LASct, left atrial strain during contraction phase; LASr, left atrial strain during reservoir phase; LV-GLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro B-type natriuretic peptide; RWT, relative wall thickness. ¶Paired *t*-test, **Wilcoxon Signed Ranks Test.

199.9 ± 21.17 to 186.24 ± 16.77 ($P < .001$) (Table 4). Left ventricular mass index decreased in the control group also but failed to reach statistical significance.

Left atrium strain values significantly improved with LA reservoir strain increasing from 28.74 ± 9.31% to 36.39 ± 12.3% ($P < .001$), LA contractile strain from −12.8 ± 5.41 to −17.89 ± 6.85 ($P < .001$) and conduit strain from −15.97 ± 5.49 to −22.5 ± 8.25 ($P < .001$) in the dapagliflozin group (Table 4, Figure 1A and B). Improvement in LA strain values was also noted in the control group but could not reach statistical significance. The changes in LA reservoir strain were the most significant determinant for the improvement in LAEF after administration of SGLT-2 inhibitors [Spearman's coefficient correlation r(s) = 0.543, $P < .001$], followed by change in LA contractile strain [r(s) = 0.530, $P < .001$] and LA conduit strain [r(s) = 0.345, $P < .015$] (Table 5, Figure 2). Although LAEF is a characteristic of LA booster pump function, good correlations could be demonstrated between LAEF and LA reservoir strain, LA conduit strain as well as LA contractile strain. By multiple linear regression analysis, changes in the LA reservoir strain and LAEF were the most predominant variables that significantly increased in the study group as compared to the control.

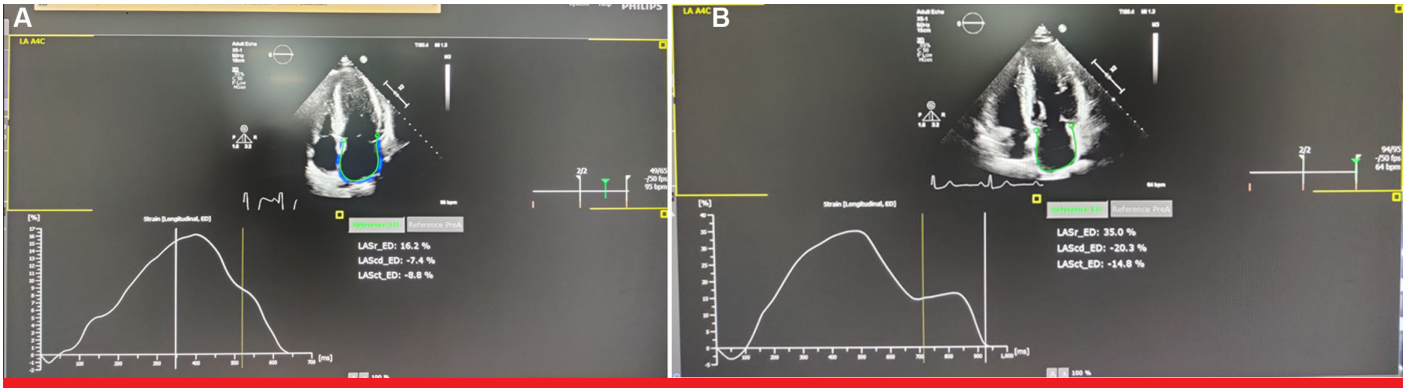

Figure 1. (A) Strain curve at baseline before treatment with SGLT-2 inhibitor. Reservoir strain is measured as the difference between the peak strain curve value and baseline (positive value). Conduit strain is calculated as difference of the strain value at the onset of atrial contraction minus the peak strain value (negative value). Contractile strain is calculated as difference of the strain value at baseline minus the strain value at the onset of atrial contraction (negative value). (B) Six months after treatment with dapagliflozin, reservoir strain changed from 16 to 35, conduit strain increased from −7.4 to −20.3 and contractile strain also increased from −8.8 to −14.8.

Table 5. Correlation of Improvement in Left Atrial Ejection Force (%) with Improvement in Left Ventricular Global Longitudinal Strain (%), Left Atrial Strain During Reservoir Phase, Left Atrial Strain During Conduit Phase, and Left Atrial Strain During Contraction Phase

Variables	Improvement in LV-GLS (%)	Improvement in LASr (%)	Improvement in LAScd (%)	Improvement in LASct (%)
Improvement in LAEF (%)				
Correlation coefficient	0.138	0.543	0.345	0.530
P	.339	<.001	.015	<.001

Spearman rank correlation coefficient. LASct, left atrial strain during contraction phase; LASr, left atrial strain during reservoir phase; LV-GLS, left ventricular global longitudinal strain.

Left Ventricle Global Longitudinal Strain

Left ventricle global longitudinal strain showed significant improvement from −15.9 ± 4.13 to −17.1 ± 3.53 (*P* < .001) after 6 months of dapagliflozin therapy in the study group (Table 4). Left ventricle global longitudinal strain improved in the control group also but failed to reach statistical significance.

Intraoperator reproducibility was excellent for all 2D-STE variables: intraclass Spearman's correlation coefficient r(s) = 0.99 (IQR: 0.99-0.99) for LVGLS, and 0.98 (IQR: 0.97-0.99) for LA strain. All variables showed an improvement in both study groups; however, the changes were higher in the dapagliflozin group than in the control group and reached statistical significance.

Plasma N-Terminal Pro B-Type Natriuretic Peptide

Patients in the study group had a significant reduction in NT-ProBNP value from a baseline mean value of 336 (180.715-514.375) to 128 (108.5-230) after 6 months of dapagliflozin therapy (*P* < .001) (Table 4).

In the study group, only 4 patients experienced side effects, including urinary tract infection (n = 1), myalgia (n = 1), and nausea (n = 2). New York Heart Association class improved after treatment in both groups; however, the change was higher for patients treated with dapagliflozin than GDMT alone. There was a statistically significant difference in patients showing improved symptoms in the study group as compared to the control group (92.1% versus 67.2%, *P* < .01). On follow-up of 6 months, there were 5 episodes of HF hospitalizations only in the control group, but no hospitalizations were reported in the study group. There was no mortality reported in either group.

DISCUSSION

Heart failure with preserved ejection fraction constitutes more than 50% of all heart failure cases and has emerged as a significant public health concern in recent years.[1,2] A primary pathological feature observed in HFpEF is LV diastolic dysfunction. The LA plays an essential role in facilitating LV filling during diastole. LA function is typically categorized into 3 distinct phases: first, the reservoir phase, during which the LA stores pulmonary venous return while the LV contracts and undergoes isovolumetric relaxation. Second, the conduit phase, where the LA allows passive blood flow into the LV. Finally, during the booster pump phase, the LA contracts actively at the end of diastole, contributing 15-30% of the LV stroke volume.[25] Comprehensive assessment of all LA functions using a single metric is challenging due to the complexity of LA contractile performance, which depends

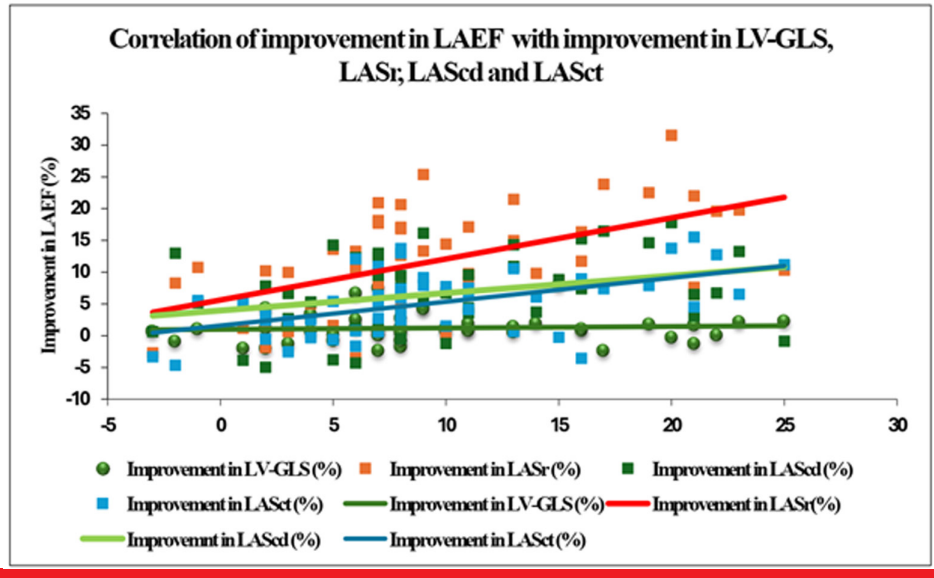

Figure 2. Scatter plot displaying the correlation of improvement in LAEF (%) with other variables (LV-GLS, LASr, LAScd, LASct). LAEF, left atrial ejection force; LAScd, left atrial strain during conduit phase; LASct, left atrial strain during contraction phase; LASr, left atrial strain during reservoir phase; LV-GLS, left ventricular global longitudinal strain.

on factors like LA preload, the force driving blood through the mitral valve, and LV end-diastolic pressure. Studies have shown that LA dysfunction is frequently observed in HFpEF patients, often associated with LV diastolic dysfunction.[26,27] Impairment of LA function in patients with HFpEF continues to remain a matter of debate because of this close intricate relationship between LA function and LV diastolic function.

The assessment of LA function in patients with HFpEF has not been extensively explored. One parameter, LAEF, measures the force generated by the LA during LV filling, yet it remains underrepresented in existing literature. This study aims to evaluate LAEF as an additional diagnostic marker for HFpEF and to analyze how dapagliflozin influences LAEF, along with changes in LA and LV strain parameters. The concept of utilizing LAEF to evaluate LA systolic function was first introduced by *Manning et al* in 1993.[28] Their approach relied on Newtonian principles, using area (mitral valve area) and velocity (trans-mitral A wave) to calculate force. They concluded that LAEF serves as a physiological indicator of atrial systolic performance and provides a valuable measure of the LA role in diastolic function. Notably, LAEF tends to increase from grade I to grade II diastolic dysfunction but shows a significant decline in grade III diastolic dysfunction. This drop is associated with pronounced LA dilation and failure, where the LA primarily functions as a conduit, exhibiting substantial impairment in its contractile ability.[27]

Initially designed for the treatment of T2DM, SGLT-2 inhibitors have now become a cornerstone in the management of HFrEF. The recently published 2023 focused update of the 2021 ESC guidelines on heart failure has awarded a class IA recommendation to SGLT-2 inhibitors, endorsing them as the first-line therapeutic agents for heart failure regardless of diabetes status.[14] This randomized study assessed the impact of the SGLT-2 inhibitor dapagliflozin on LAEF, LA and LV strain parameters over 6 months in patients with HFpEF. The main findings from the study include,

a. A significant reduction in LAEF following dapagliflozin therapy, suggesting its role in promoting reverse remodeling of the LA in HFpEF patients ($P < .001$).
b. Marked improvements in LA reservoir strain, LA contractile strain, and LA conduit strain after 6 months of therapy (all $P < .001$).
c. Significant enhancements in LV global longitudinal strain (LV-GLS) ($P < .001$).
d. A notable decrease in NT-ProBNP levels in the study population ($P < .001$).

Therapy with SGLT2 inhibitors has been shown to significantly improve 2D-STE variables in HFpEF patients, demonstrating a favorable therapeutic response. The reduction in LAEF, coupled with enhanced strain parameters, suggests that LAEF, like strain values, can serve as an early and reliable indicator for the diagnosis and treatment of HFpEF. Both 2D-STE and LAEF offer non-invasive, efficient, and cost-effective methods for assessing myocardial function. A study by Piros et al,[29] involving 33 patients, revealed a correlation between LAEF and global LA 3D strain. Additionally, Thiele et al[30] reported that SGLT-2 inhibitors significantly improved LA reservoir and contractile strain after 3 months of therapy compared to placebo in patients with T2DM. A prospective study by El-Saied et al[8] demonstrated substantial improvements in all LA function parameters, including LA emptying velocity and strain values, in patients with heart failure with mildly reduced ejection fraction, achieving statistical significance ($P < .001$). Consistent with these findings, the current study also observed significant enhancements in LA strain parameters, including an increase in LA reservoir strain from $28.74 \pm 9.31\%$ to $36.39 \pm 12.3\%$, LA contractile strain from -12.8 ± 5.41 to -17.89 ± 6.85, and LA conduit strain from -15.97 ± 5.49 to -22.5 ± 8.25 (all $P < .001$). These results suggest that dapagliflozin improves LA contractile function and promotes reverse remodeling, which concurrently leads to a reduction in LAEF also.

While LAEF primarily reflects the booster pump function of the LA, it also shows a correlation with LA reservoir strain. Multivariate linear regression analysis in the study identified changes in LA reservoir strain as the most significant variable, showing a marked increase in the treatment group compared to the control. LA reservoir strain has established itself as a reliable marker of LV filling pressures and diastolic function. Its importance has been recognized and incorporated into the diagnostic algorithm for HFpEF by the American Association of Cardiovascular Imaging.[31]

Left ventricular global longitudinal strain has proven to be a reliable predictor of early LV reverse remodeling, likely due to its correlation with the extent of myocardial fibrosis. This highlights the potential of SGLT-2 inhibitors to promote LV reverse remodeling in heart failure beyond improving ejection fraction, with possible enhancements in LV function that may lead to better clinical outcomes and reduced risk of future events. SGLT-2 inhibitors have also demonstrated the ability to modulate inflammatory pathways by decreasing circulating cytokine levels, oxidative stress, and fibrosis—key contributors to diastolic dysfunction and HFpEF.[32]

The DAPA MODA (Impact of Atrial Remodeling of Dapagliflozin in Patients With Heart Failure) study showed that dapagliflozin therapy in chronic HF patients leads to global reverse remodeling, including reduced LA volumes and improved LV geometry.[33] Similarly, a study by Tanaka et al[34] found that LV-GLS improved significantly in patients with T2DM and stable HF after 6 months of dapagliflozin treatment. HFpEF patients experienced a greater improvement in GLS, which increased from 17.0% to 18.7% ($P < .001$). In the current study also, dapagliflozin was associated with a significant improvement in LV-GLS, which increased from -15.9 ± 4.13 to -17.1 ± 3.53 ($P < .001$), underscoring its role in promoting cardiac reverse remodeling in HFpEF patients.

The DAPA ECHO trial further examined the effects of dapagliflozin on myocardial deformation using 2D-STE in nondiabetic patients with an LV ejection fraction <50%. It demonstrated early improvements in cardiac functional remodeling, including enhancements in LV, LA, and right ventricular geometry, as well as significant changes in 2D-STE parameters. The trial emphasized the utility of dapagliflozin in improving outcomes for patients with HFrEF

and heart failure with midrange ejection fraction (HFmrEF). Importantly, the DAPA ECHO trial highlighted the value of 2D-STE not only as a diagnostic tool but also for monitoring therapeutic responses in HF patients.[35]

Compared to LV-GLS, the more pronounced improvement in LA strain and significant reduction in LAEF observed in patients treated with dapagliflozin for HFpEF supports the hypothesis that these may be the most reliable echocardiographic parameters for assessing treatment efficacy, particularly in improving congestive symptoms, regardless of LV ejection fraction. This is consistent with the idea that the LA may be primarily affected by "intrinsic atrial myopathy," which can occur independently of the extent of LV dysfunction. Additionally, LA function is closely tied to LV compliance, which reflects diastolic function rather than systolic performance.[26,36] Several studies have highlighted that LA strain serves as a key predictor of LV filling pressures, patient prognosis, and functional capacity in HF, irrespective of ejection fraction. The observed improvements in LA strain parameters and reduction in LAEF could result not only from the positive effects of SGLT-2 inhibitors on left cardiac functional remodeling but also from its natriuretic and osmotic diuretic effect.

Pastore et al[37] reported that dapagliflozin alleviated congestive symptoms in patients with HFrEF and HFmrEF, as evidenced by reductions in E/e' ratio, systolic pulmonary artery pressure, and NT-proBNP levels, without significant effects on systolic or diastolic blood pressure.[37] Similarly, the present study found reductions in NT-proBNP levels alongside improvements in key cardiac parameters, including LAVI, LV-GLS, LA strain, and LVMI. These findings underscore the beneficial effects of dapagliflozin on heart failure symptoms and cardiac function, particularly in HFpEF management. Furthermore, the DACAMI (Impact of Dapagliflozin on Cardiac Function in Non-Diabetic Patients) trial demonstrated that nondiabetic patients with myocardial infarction and an LVEF <50% experienced significant reductions in NT-proBNP levels and LVMI when treated with dapagliflozin compared to placebo. This further highlights the potential of dapagliflozin to enhance cardiac function in a broad range of patients.[38]

To the best of our knowledge, this is the first study to evaluate the effects of dapagliflozin on LAEF alongside routine echocardiographic parameters and strain assessments of the LA and LV in patients with HFpEF. The observed reduction in LAEF reinforces the notion of LA dysfunction in HFpEF, highlighting the early development of atrial myopathy in these patients. Notably, the enhancement in LAEF was observed in both diabetic and non-diabetic patients, with a positive correlation to LA strain parameters in the study group. These findings suggest that, in addition to routinely performing 2D-STE for assessing LA and LV strain parameters, calculating LAEF can provide valuable diagnostic support for HFpEF. LAEF calculation is straightforward and offers a practical alternative in settings where strain analysis is not available. It can aid in evaluating atrial dysfunction and strengthening the diagnosis of HFpEF. Establishing a standardized cut-off value for LAEF through larger studies could solidify its role as a diagnostic tool for HFpEF.

Study Limitations

The present findings should be interpreted with several potential limitations in mind. The study's relatively small sample size of 100 patients from a single center and a short follow-up of 6 months only may not fully represent the broader population of HFpEF patients. Therefore, future randomized controlled trials with larger sample sizes are needed to validate these results and investigate the long-term effects of dapagliflozin on HFpEF. Advanced cardiac imaging modalities such as 3-dimensional echocardiography and cardiac magnetic resonance imaging were not used. The formula for estimating LAEF considers the mitral valve to be circular while it is actually elliptical. This is not going to affect the findings as the same method was obtained for all patients. The dependence of STE on image quality and correct acquisition should be considered.

CONCLUSION

Dapagliflozin leads to a significant reduction in LAEF along with improvement in LA strain and LV-GLS, thus reaffirming its role in LA and LV reverse remodeling in patients with HFpEF. In the setting where LA strain assessment is not easily available, LAEF can guide us in assessing atrial dysfunction and in establishing the diagnosis of HFpEF. Considering its favorable safety profile and significant observed benefits, dapagliflozin is a suitable addition to conventional drug therapy for the management of HFpEF patients.

Ethics Committee Approval: The study was approved by the Institutional Ethical Committe of Maulana Azad Medical College, New Delhi, India. Approval number - F.1/EC/MAMC/104/10/2023/no.46. It was approved on 27 March 2024.

Informed Consent: Written informed consent was obtained from all participants prior to inclusion in the study.

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