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ORIGINAL ARTICLE

Effect of Sodium Glucose Transporter 2 Inhibitor (SGLT2i) on Peak Left Atrium Strain in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF) and its Correlation with N - Terminal Pro B Type Natriuretic Peptide (NT pro BNP) Level : A Follow Up Study

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2i) inhibitors were initially introduced as oral hypoglycaemic agents. These medications have demonstrated effectiveness in reducing hospitalisations for heart failure and offer mortality benefits for individuals with type 2 diabetes and cardiovascular disease. Left atrial (LA) dysfunction is now considered to play a major role in the pathogenesis of Heart Failure with preserved Ejection Fraction (HFpEF). SGLT2 inhibitors are proved to improve cardiac remodelling irrespective of glycemic profile and reduce Left Atrial Volume Index (LAVI) with treatment. The aim of the study is to determine the effect of SGLT2i on LA strain in patients with HFpEF. This is a descriptive follow-up study, conducted at Cardiology IPD & OPD, IPGMER and SSKM Hospital, Kolkata, which aims to evaluate the effects of SGLT2 inhibitors on patients with heart failure with preserved ejection fraction (HFpEF). It involves 50 patients presenting with HF symptoms and an H2FPEF score ≥ 6. The study includes a baseline assessment with detailed history, NT-proBNP levels, and echocardiography (including LV global longitudinal strain, LA strain, RV function, and diastolic parameters). After 6 months of treatment with SGLT2 inhibitors, patients will undergo a follow-up evaluation using biomarkers and electrocardiographic parameters like LV volumes, LV diastolic function, LV Global Longitudinal Strain, LA Strain. Statistical analysis was performed using SPSS, with significance set at a p-value ≤ 0.05. In our study, the mean age of the population is 61.64 ± 8.69years. 34% of the population had atrial fibrillation, 72 % were obese, 10% belonged to NYHA Grade III. 38% of the patients were given Empagliflozin and 62% were given Dapagliflozin. In our study, we found that treatment with SGLT2i resulted in significant improvement in LAVI from 48 ± 2.4 ml/m2 to 41.8 ± 2.9 ml/m2, peak LA strain and E/e'. Peak LA strain showed a negative correlation with NT Pro BNP level.

Keywords: SGLT2 inhibitors (SGLT2i); Heart Failure; LA dysfunction; LA Strain; NT ProBNP; Cardiac remodelling; Echocardiography

INTRODUCTION

HFpEF is a heterogeneous group of disorders associated with significant morbidity and mortality. It has been linked with comorbidities like hypertension, obesity, diabetes, CAD, CKD and rarely, cardiac amyloidosis [1]. According to the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, HFpEF is diagnosed as LVEF $\geq$50% with evidence of cardiac dysfunction by echocardiography and elevated biomarkers [2]. Different scores like H2FPEF and HFA PEFF score are used for diagnosis of HFpEF. With a score of >/ 6 in H2FPEF, heart failure is diagnosed with a probability of

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>90%.

Sodium-Glucose co-transporter 2 inhibitors (SGLT2i) are oral hypoglycaemic agents which act on the SGLT-2 proteins expressed in the proximal convoluted tubules (PCT). The SGLT2 inhibitors in the HFpEF were a class IIA recommendation in the previous guidelines[3]. But in the 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, SGLT2i have got class I recommendation for management of HFpEF. The left atrium (LA) plays pivotal role in LV filling during the diastole. Its dysfunction is a strong predictor of heart failure (HF), atrial fibrillation, and even cardiovascular death[4]. Left atrial dysfunction is now considered to play a major role in the pathogenesis of HFpEF.

SGLT2 inhibitors are proved to improve cardiac remodelling irrespective of glycemic profile and reduces E/e' and LAVI with treatment[5].

Strain imaging by 2DSTE provides accurate and quantitative assessment of myocardial deformation of cardiac chambers.Though in patients with HFpEF LV filling pressure is normal at rest, it may increase with exercise, and LA strain corroborates well with this exercise induced increase in LV filling pressure[6].

As diastolic dysfunction is the main pathology in patients with HFpEF, this study looks for the effect of treatment with SGLT-2 inhibitors on diastolic functions in patients with HFpEF through the assessment of LA function by 2D- STE.

Aim

- Determine the effect of SGLT2i on LA strain in patients with HFpEF.

Objectives

- To determine effect of SGLT2i on NT pro BNP level in patients with HFpEF.
- To establish any correlation between NT pro BNP and peak
- LA strain and also to establish between different diastolic functional parameters and strain parameters.
- To determine effect of SGLT2i on LV diastolic function in patients with HFpEF.
- To determine the effect of SGLT2i on LV GLS in patients with HFpEF.
- To determine the effect on SGLT2i on RV function.

MATERIALS AND METHODS

- **Study area**: Cardiology IPD& OPD of IPGMER and SSKM Hospital, Kolkata.
- **Study period**: 12 months (6 month follow up).
- **Study design**: Descriptive follow up study.
- **Study setting**: This is a single-centre study, which will take place at IPGME&R, Kolkata.
- **Study duration**: February 2023 to February 2024.

Study population

Inclusion criteria

- Patient presenting in cardiology IPD/OPD with symptoms of heart failure with H2FPEF score ≥6.

Exclusion criteria

- Acute coronary syndrome, stroke or transient ischaemic attack within 90 days
- Acute decompensated heart failure
- Pregnancy/lactation
- eGFR<20ml/min/1.73m2 known allergic reaction to SGLT2i
- Diabetic patients who are already on SGLT2i.

Sample size

Considering prevalence of HFpEF is 5.2% in India with confidence interval keeping at 95% with margin of error 5% estimated sample size is 73. However, considering time constraints we opt to keep our sample size 50.

Study Technique

Patients with HFpEF meeting inclusion criteria and free from exclusion criteria will provide informed consent and undergo baseline assessments, including history, physical exam, NT pro BNP levels, and echocardiography (for LA Strain, LVGLS, RV function, and diastolic function). They will then be treated with SGLT2 inhibitors for 6 months, after which biomarkers and echocardiographic parameters will be reassessed.

- All the echocardiographic measurements were obtained according to current guidelines of the American Society of Echocardiography / European Association of Cardiovascular Imaging[7].
- LV End Systolic, End diastolic and Ejection Fraction were estimated using Simpson's Modified Biplane Method.
- LV diastolic function was determined using trans mitral inflow velocities, assessed by pulsed wave Doppler, the E/A ratio, and the pulsed(e') diastolic velocity wave issue doppler.
- The E/e' ratio was calculated as the measure of the LV filling pressure.
- PASP was assessed through the evaluation of peak tricuspid regurgitation velocity (TRV). PASP = RA pressure $+4V^2$, where V = TRV.
- LVGLS (Left ventricular global longitudinal strain) was obtained by tracing endocardial borders manually and incorporating them in a software which calculated the regional average of the apical two chamber, four chamber and three chamber views of the 17 segments at an end-systolic frame.

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- Deformation analysis of the LA was performed by 2D STE on focused 4- chambers and 2-chambers, at a frame rate 60-80 frames/sec, using an automated software. The baseline LA strain reference was set at ventricular end diastole using R-R ECG gating.

Statistical Analysis

Data will analyzed using the SPSS 20.0 software (IBM, NY, USA) Continuous variables will be represented as Mean, Standard Deviation (SD) or Coefficient of Variation (CV). Statistical significance of study parameters on categorical scale between two or more groups will be studied using the independent t-tests, Chi-square test or Fischer exact test P value of $\leq$ 0.05 will indicate statistical significance Correlation between two parameters will be studied using the Pearson/ Spearman Correlation coefficient. Regression analysis will be used wherever required.

RESULTS AND OBSERVATION

Out of 50 patients, 36 % of the patients were in the age group 61-70 years followed by 34% in the age group 51-60 years. The mean age of our study population was found to be 61.64 $\pm$ 8.69years. 56% of the patients were male, rest 44% were female. 44% patients had history of smoking, rest were non-smoker. Only 34% of patients had Atrial Fibrillation. Out of 50 patients, 38% of the patients were given the drug Empagliflozin and 62% of the patients were given Dapagliflozin. 90% of the patients were classified as NYHA Class II and only 10% were categorised as NYHA Class III.

Table 1: Comparison between NT Pro BNP (0 month) with NT Pro BNP (6 months)

Group Statistics					
	Group	N	Mean	Std. Deviation	p-value
NT Pro BNP	0 month	50	651.116	28.576	0.001
	6 months	50	625.836	44.7152	

P<0.05 — significant difference in mean value

Table 2: Comparison between E/e' (0 month) with E/e' (6 months)

Group Statistics					
	Group	N	Mean	Std. Deviation	p-value
E/e'	0 month	50	13.476	1.5404	<0.0001
	6 months	50	10.466	0.9184	

P<0.05 Significant difference in mean value

Comparison between LVEF, TAPSE, RV strain, E/A, E/e', PASP, eGFR, SBP, DBP, BMI showed no significant difference at 0 month and 6 month.

Table 3: Comparison between LVGLS (0 month) with LVGLS (6 months)

Group Statistics					
	Group	N	Mean	Std. Deviation	p-value
LVGLS	0 month	50	- 16.10	4.74	0.014
	6 months	50	- 17.78	0.11	

P<0.05 - Significant difference in mean value

Table 4: Comparison between LAVI (0 month) with LAVI (6 months)

Group Statistics					
	Group	N	Mean	Std. Deviation	p-value
LAVI	0 month	50	48.598	2.4453	<0.001
	6 months	50	41.890	2.9005	

P value<0.05 Significant difference in mean value

Table 5: Comparison between Peak LA strain (0 month) with Peak LA strain (6 months)

Group Statistics					
	Group	N	Mean	Std. Deviation	p-value
Peak LA strain	0 month	50	-12.9048	1.18543	<0.001
	6 months	50	-17.6758	1.81224	

P value <0.05 Significant difference in mean value

DISCUSSION

A prospective study evaluated the effects of SGLT2 inhibitors (SGLT2i) on peak left atrial (LA) strain, left ventricular (LV) global longitudinal strain (GLS), right ventricular (RV) function, and diastolic function in patients with HFpEF. The mean age of the 50 patients was 61.64 $\pm$ 8.69 years, with a higher proportion (36%) in the 61-70 age group. The study population was predominantly male (56%) and obese (72%). At baseline, the mean NT-proBNP was 651 $\pm$ 28.57 pg/ml, which significantly reduced to 625.82 $\pm$ 44.71 pg/ml after 6 months (p=0.001).

LV GLS improved significantly from -16.10 $\pm$ 4.7 to -17.78 $\pm$ 3.1 (p=0.014), while LA strain also showed a significant improvement, from -12.90 $\pm$ 1.18 to -17.67 $\pm$ 1.81 (p<0.001).

However, RV function, assessed by TAPSE and RV strain, did not show significant changes. The diastolic function parameter E/e' improved significantly from 13.4 $\pm$ 1.5 to 10.4 $\pm$ 0.9 (p<0.001), but E/A did not show any significant improvement.

There was no significant change in blood pressure (SBP: 148.8 $\pm$ 14.7 to 147.0 $\pm$ 14.0 mmHg; DBP: 85.8 $\pm$ 10.8 to 84.3 $\pm$ 10.1 mmHg). The BMI remained relatively stable, with a minor reduction from 29.8 $\pm$ 7.1 to 29.6 $\pm$ 7.2 kg/m^2. LAVI significantly improved from 48 $\pm$ 2.4 to 41.8 $\pm$ 2.9

ml/m^2 (p<0.001). eGFR remained stable, with no significant changes (66.4 $\pm$ 7.9 to 66.7 $\pm$ 5.2 ml/min/m^2; p=0.808), supporting the renal safety of SGLT2i.

Correlation analysis showed positive correlations between LA strain and LV GLS, and between LAVI and E/e', while peak LA strain negatively correlated with both LAVI and E/e'. These findings are consistent with previous studies. In terms of safety, no harmful effects on kidney function were observed, aligning with prior evidence of SGLT2i's renal and cardiovascular protective roles.

A meta analysis of two major trials EMPA KIDNEY[8] and DELIVER[9] have proved its renoprotective role and cardioprotective role.

SUMMARY AND CONCLUSION

This study assessed the effects of SGLT2 inhibitors in patients with HFpEF over six months. We found significant improvements in left atrial volume index (LAVI), peak LA strain, and E/e', while no improvement was seen in E/A or RV function (TAPSE and RV S'). Although left ventricular ejection fraction (LVEF) remained s t able, LV global longitudinal strain (LV GLS) improved significantly, accompanied by a notable reduction in NT-proBNP. Blood pressure (SBP, DBP) and pulmonary artery systolic pressure (PASP) showed slight, statistically insignificant decreases. Kidney function, measured by eGFR, remained stable. Correlation analysis revealed a negative correlation between peak LA strain and NT-proBNP levels, while peak LA strain positively correlated with LV GLS and LAVI, and negatively with both LAVI and E/e'.

LIMITATIONS

The limitations of the study are as follows:

- Non-randomised, single-centre design.
- Modest sample size.
- Relatively short follow-up period.
- LA volume calculated using a two- dimensional method; three-dimensional measurement is more accurate.
- Did not measure LA reservoir, LA conduit, and LA contractile strain separately, instead using peak LA strain.

Conflict of Interest

None.

Source of funding

Self.

Authors Contribution

Dr. Abhishek Naskar- Concept and study design, data acquisition, and article drafting. **Dr. Pradip Kumar Ghoshal**- Concept and study design, analysis, and interpretation of data, drafting the article. **Dr. Subhrangsu Chatterjee**- analysis, and interpretation of data, revising draft critically for important intellectual content, final approval of the version to be published. **Dr. Rajarshi Mondal**- Concept and study design, data acquisition, analysis, and interpretation of data. **Dr. Tanmoy Knati Goswami**- revising draft critically for important intellectual content, final approval of the version to be published. **Dr. Asish Biswas**- revising draft critically for important intellectual content, final approval of the version to be published.

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