

Effects of Dapagliflozin on Right Ventricular Function Assessed by Different Echocardiographic Parameters in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce cardiovascular events in patients with type 2 diabetes (T2DM) and are associated with a reduction in left ventricular (LV) mass index. However, the impact on right ventricular (RV) remodeling is unknown. Dapagliflozin was proven to decrease cardiovascular death, heart failure hospitalization in patients who have an ejection fraction of 40% or less. However the impact on patients who have preserved ejection fraction is not yet proven, there have been many advances in noninvasive RV imaging during the past decade, echocardiography remains the most accessible and easiest method to assess RV volumes and functions.

Aim of Study: This study aimed to examine the effect of dapagliflozin on RV function assessed by different methods in patients with heart failure with preserved ejection fraction (HFpEF) and T2DM at baseline and after 6 months of treatment.

Patients and Methods: This study was carried-out on 40 patients with definite diagnosis of HFpEF. The patients were collected from Al-Arish University Hospital (Cairo, Egypt). All patients included in the study were subjected to different echocardiography parameters, both conventional parameters right ventricle / left ventricle diameter ratio, RV fractional area change, tricuspid annular plane systolic excursion (TAPSE), tricuspid valve (TV) TDI velocity, and RV speckle tracking parameters (RV global strain (RV GS) and RV free wall strain before treatment and after 6 months of medical treatment that include dapagliflozin.

Results: All echocardiographic parameters mean \pm SD assessed in blinded fashion at baseline as follow TAPSE (17.02), FAC (33.85%), RV diameter/LV diameter ratio >1 (52.5%), RVOT Systolic excursion (4.55mm), RV GS (-17.17). RV free wall strain (-21.17), PAP (32mmHg) and after using the dapagliflozin were TAPSE (20.97), FAC (36.9%) RV diameter/

LV diameter ratio >1 (not recorded), RVOT Systolic excursion (5.52mm), RVGS (-20.7), RV free wall strain (-24.72), PAP (20mmHg). There was significant correlation between effects of using dapagliflozin on RV improvement changes from baseline to 6 months.

Conduction of this Study: This study concluded that treatment with dapagliflozin for diabetic patients type 2 with HFpEF enhanced the RV systolic function measured by different echocardiography parameters.

Key Words: Dapagliflozin — RV-speckle tracking — HFpEF.

Introduction

HEART failure with preserved ejection fraction influences half of all patients with heart failure (HF). While formerly neglected, the right ventricle has sparked importantly in recent years. Right ventricular disorder (RVD) is found in 4%-50% of patients with HFpEF [1].

Dapagliflozin is an inhibitor of sodium-glucose co-transporter-2, the transporters ordinarily answerable for the re-absorption of glucose within side the kidney. It is used clinically as an accessory to weight loss. More recently, the use of empagliflozin and dapagliflozin changed to be used now in patients with heart failure with reduced ejection fraction (HFrEF) without or with type 2 diabetes mellitus [2]. The mechanism of these benefits, especially on decreasing HF hospitalizations and cardiovascular death remains uncertain. It may be related to decreased inflammation, the extracellular matrix and fibrosis [3].

The sodium-glucose cotransporter 2 inhibitor empagliflozin and dapagliflozin were proven to reduce all-cause mortality and heart failure hospitalization in patients with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD) who have an ejection fraction of 40% or less [4]. Other SGLT2 inhibitors have also been evalu-

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ated in large cardiovascular (CV) outcome trials in those at risk for, or with established ASCVD, and have shown similar results [5].

More recently, the benefit of dapagliflozin and empagliflozin was confirmed in patients with HF with reduced ejection fraction with or without T2DM [6]. The mechanism of these benefits, particularly on reducing HF hospitalizations and CV death, remains unclear. In diabetic kidney disease dapagliflozin was associated with attenuated or decreased levels of biomarkers that suggest an effect on molecular processes related to inflammation, the extracellular matrix and fibrosis [3]. Other proposed mechanisms of SGLT2 inhibition include natriuretic, osmotic diuresis, a reduction in preload and after load, and inhibition of the cardiac sodium-hydrogen exchanger. However, whether and how these mediators alter cardiac structure and function remain incompletely understood [3].

Aim of the work:

This study aimed to study the effect of dapagliflozin on RV function measured by different methods including speckle tracking in patients with HFpEF and type 2 diabetes mellitus.

Patients and Methods

This study was carried-out on 40 patients with definite diagnosis of HFpEF; the patients were collected from Al-Arish University Hospital from 1st of June 2021 to 31st of January 2022.

The purpose and design of the study were explained to the patients and the family members. The confidentiality of information obtained was maintained and revealed only to the doctor/auditor involved in the study and to regulatory authorities. The study was conducted on ethical guidelines for Biomedical Research on human subjects given by Central Ethical Committee on Human Research, New Delhi, in addition to principles enunciated in the "Declaration of Helsinki".

All patients included in the study subjected to different parameters of echocardiography include both conventional parameters and RV speckle tracking parameters before treatment and after 6 months of slandered recommended dose 10mg once daily of dapagliflozin.

Inclusion criteria:

Patients with definite diagnosis of HFpEF (that defined according to ESC guidelines 2023 that patients have symptoms and signs of HF and EF <50%) were included in the study [7].

Exclusion criteria:

All of the following patients were excluded from the study: Patients with obstructed cardiomyopathy, patients with permanent pacemakers (PPM),

atrial fibrillation (AF), and moderate to severe valvular heart disease, pregnant patients, and patients with poor echogenic window.

All patients underwent the following:

- *Full history, clinical examination, and 12-lead Electrocardiogram (ECG):*

Age, sex, history of risk factors as hypertension, smoking, diabetes, hypercholesterolemia, obesity, positive family history of ischemic heart disease (IHD), history of IHD, general full examination and local cardiac examination, ECG.

- *Laboratory investigation:*

Include liver function, renal function, complete blood count, coagulation profile and serum electrolytes.

- *Echocardiographic evaluation:*

- Measurement of LV systolic function using conventional techniques and measurement of right ventricle/left ventricle diameter ratio which normally less than one [8].
- RV Fractional area change was measured using RV focused apical four-chamber view the American Society of Echocardiography and the European Association of Cardiovascular Imaging in 2015 described the normal range for RV-FAC, and a value of <35% was taken as suggestive of RV systolic dysfunction [8].
- Tricuspid annular plan systolic excursion (TAPSE) was measured using M-mode echocardiography, normal values are more than 18mm [8].
- Tissue Doppler image (TDI)-lateral e' tricuspid annular velocity and normal range above 11 cm/S [9].
- TV TDI S' velocity was measured by recording the peak systolic velocity at the lateral tricuspid valve annulus using TDI, normal range 13-15cm/S [9].
- RV global longitudinal strain (GLS): There are two types: RV-GLS total and RV-GLS free wall. RV-GLS total includes the strain value of the ventricular septum added to RV-GLS free wall. The exclusion of the inter-ventricular septum in RV-GLS free wall is based on the consideration that it reflects both right and left systolic function. However, systolic inter-ventricular dependence greatly contributes to RV longitudinal shortening [10].
- In this study, RV-GLS total was measured. Frame rate was kept between 60 and 90/min, and RV-focused apical four-chamber view was used. The machine used was GE vivid E 90 machine, Lowest expected normal value of RV global strain was -17% and lowest expected normal value for RV free wall strain was -19% [11].
- RVOT Systolic excursion (SE) less than 5mm was 80% sensitive and 76% specific to identify patients with impaired RV function [10].

Statistical methods:

Descriptive statistics for categorical variables were reported as frequency and percentage, whereas continuous variables were reported as mean and standard deviations. Comparisons between the echocardiographic parameters measured before and after treatments were carried out using paired t-test. Also, Chi²-test used for percentage comparison.

Results

Baseline characteristics of the study population (Table 1):

The mean \pm SD age of this study population was ± 61.15 year. All patients included in this study had preserved left ventricle ejection fraction (LVEF) $\geq 50\%$, the mean \pm SD of LVEF $\pm 58\%$. Male patients were 23 (57.5%) and female were 17 (42.5%).

Diabetes mellitus observed in 40 (100%), hypertension observed in 33 (82.5%) and the number of smokers were 30 (75%). The dyslipidemia observed in 35 (87.5%) of the examined patients while, those suffering from obesity reached to 34 (85%).

While the patients suffering from coronary artery disease (CAD) reached to 31 (77.5%), and chronic kidney disease (CKD) their number reached to 7 (17.5%).

Effect of treatment by dapagliflozin for 6 months:

Table (2) shows the effect of dapagliflozin on the Right ventricle (RV) function.

The systolic blood pressure before treatment was 159 while, after treatment reached to 141.4. The LVH (as cut off points to diagnose LVH is LV wall thickness in diastole > 12 mm by M mode before treatment was observed in 33 (82.5%) before treatment, and after treatment was 29 (72.5%). The TAPSE level increased from 17% to 21% after treatment. Assessment of the RV function by using speckle tracking echocardiography showed much improvement of RV function after 6 months of dapagliflozin treatment, as the RV global strain before treatment reached to -17.5% and after treatment reached to -20.7% and The RV free wall strain before treatment was -21.6% and after treatment reached to -24.7% while the FAC before treatment was 33.85% and after treatment reached to 36.9%. The RV diameter/LV diameter ratio > 1 observed in 21 (52.5%) before treatment and not recorded after treatment in any patient. The RVOT Systolic excursion before treatment was 4.5mm and after treatment reached 5.5. The TDI es lateral tricuspid annulus level was 7.2cm/s and after treatment reached to 13.2cm/s and the TDE s' TA systolic velocity was around 9cm/s before treatment and reaches to 13 cm/s after 6 months of treatment. Pulmonary artery pressure measured by echocardiography decreased from 31mmHg to 20 after treatment. No significant changes of left ventricle EF before and after 6 months of treatment.

Table (1): Population characteristics.

Variables	Number	Percentage
Male	23	57.5
Female	17	42.5
Diabetic	40	100
Hypertensive	33	82.5
Smoker	30	75.5
Dyslipidemia	35	87.5
Obesity	34	85
CAD	31	77.5
CKD	7	17.5

CAD : Coronary artery disease.

CKD : Chronic kidney disease.

LVEF: Left ventricle ejection fraction.

Table (2): Echocardiographic parameters including speckle tracking in the study population.

Variables	Before treatment	After treatment	p-value	Sig-nificant
TAPSE	17 \pm 1.8	21 \pm 2	11.89	0.0001 **
RV Global strain	-17.5 \pm 1.6	-20.7 \pm 1.9	18.42	0.0001 **
RV free wall strain	-21.6 \pm 1.6	-24.7 \pm 1.9	18.4	0.0012 **
FAC	33.8 \pm 0.7	36.9 \pm 1	66.7	0.0014 **
RV diameter/LV diameter ratio > 1	21 (52.5%)	0		***
RVOT Systolic excursion	4.5 \pm 1	5.5 \pm 0.9	7.41	0.0013 **
TDI e	7.2 \pm 1	13.2 \pm 1.8	20.78	0.0015 **
PAP	32 \pm 23	20 \pm 24	66.7	0.00012 ***

Variables	Number and percentage of patients before treatment	Number and percentage of patients after treatment	Significant
Presence of LVH	33 (82.5%)	29 (72.5%)	0.0014 **

NS = Non-significant at (p $>$ 0.05).

* = Significant at (p $<$ 0.05).

** = Significant at (p $<$ 0.01)

FAC : Functional area change.

RV : Right ventricle.

RVOT SE: Right ventricular outflow tract systolic excursion.

TAPSE : Trans-annular peak systolic excursion.

TDI : Tissue Doppler image.

PAP : Pulmonary artery pressure.

Discussion

The present study provides insights into effect of dapagliflozin on RV function in patients with HFpEF and d T2DM. Diastolic disorder is related to destructive effects and is associated with adverse outcome in heart failure with preserved ejection fraction (HFpEF) and even in healthy individuals. Dapagliflozin decreased the chance of total HF events, or recurrent in addition to initial occurrences, in individuals with HF with mildly reduced EF (HFrEF) or heart failure with preserved ejection fraction (HFpEF) [12].

Our study showed that the baseline characteristics of the patients with HFpEF commonly observed in patients with old age specifically at 60 years or greater, and in male more than female. Also, in smoker patients and patients with diabetes, hypertension, dyslipidemia, obesity, CAD and CKD.

In terms of structure, function, loading circumstances, and disease adaptability, the RV differs significantly from the LV [13]. Importantly, there's a paucity of records on how SGLT2 inhibition impacts the morphology and characteristic of the RV [14].

Regarding age and comorbidities our result was concordant with the study done by Forsyth et al., 2021 [15] who stated that the predominant characteristics of patients with HFpEF were advanced age, and multimorbidity. The prevalence of comorbidities has been reported to be higher in HFpEF than HFrEF, consistent with the idea that comorbid conditions drive the inflammatory response leading to HFpEF [16].

Regarding gender our result was in contrast with studies done by Duca et al., [17] and Sotomi et al., [18] who stated that HFpEF affects more women than men, suggesting gender to play a major role in disease evolution. This discrepancy related to difference in sample size and variance in patients' presentation and duration of follow-up.

Our study showed that dapagliflozin improves RV characteristic: TAPSE, RV global strain, RV freewall, strain, FAC degree of RV, RVOT Systolic, and TDI degree after six month of treatment than earlier, assessment of the RV function by using speckle tracking echocardiography cleared much improvement of RV function after 6 month of dapagliflozin treatment.

Patoulas et al., [13] stated that patients with T2DM are known to have reduced RV end-systolic and end-diastolic volumes as well as impaired RV systolic and diastolic performance, even if they are newly diagnosed or do not yet have established CAD or HF. This intimate connection has also been demonstrated in individuals with concurrent T2DM and HFpEF, where T2DM is linked, independently of right ventricular after load, to a markedly increased risk of RV systolic and diastolic dysfunction. Metabolic (hyperglycemia, hyperlipidemia, and hyperinsulinaemia), inflammatory, mechanistic (left ventricular involvement), and epigenetic mechanisms have all been linked to right ventricular involvement in T2DM. As a result, right ventricular dysfunction may be a sign of diabetic cardiomyopathy.

Unfortunately, there is significant gap of knowledge about impact and beneficial effect of SGLT-2 inhibitor on right ventricular function and the subsequent cardiovascular implications [14].

Sarak et al., [19] stated that, it stays unknown whether or not Sodium-glucose co transporter 2 inhibition may also have an impact at the RV in left-sided HF with mixed pre- and post-capillary pulmonary high blood pressure.

Bami et al., [20] reported that SGLT2 inhibition may also affect ventricular interdependence via way of means of changing filling pressures, diastolic characteristic, systolic blood strain and pulmonary pressures.

Our results are considered to be in harmony with the study done by Connelly et al., [20] who studied if SGLT2 inhibition would reduce the structural, functional, and molecular responses to pressure overload of the right ventricle in thirteen-week-old Fischer F344 rats who underwent pulmonary artery banding (PAB) or sham surgery. They reported that dapagliflozin reduces the structural, functional, and molecular manifestations of right ventricular pressure overload [21].

Our study showed that, dapagliflozin improves pulmonary hypertension and reduced PAP after 6 month of treatment decreased from 31 to 20 after treatment. This result agreed with study performed by Nassif et al., [22] but different as that done on HFrEF and diabetic patients [21] they studied Sodium glucose co-transporter 2 (SGLT2) inhibitors effects on (PAP) in patients with HFrEF, In overall, 93 patients were screened, and 65 were randomized (33 to SGLT2 inhibitors, 32 to placebo), SGLT2 inhibitors significantly reduced PADP, with effects that began at week 1 and amplified over time; average PADP (weeks 8-12) was 1.5 mm Hg lower (95% CI, 0.2-2.8; p=0.02); and at week 12, PADP was 1.7 mm Hg lower (95% CI, 0.3-3.2; p=0.02) with SGLT2 inhibitors versus placebo. So, they reported that SGLT2 inhibition reduced pulmonary artery pressures unbiased of loop diuretic therapy and improved New York Heart Association (NYHA) classification in patients with HFrEF [22].

Conclusion:

The use of dapagliflozin improve the RV characteristic and function including TAPSE, RV global strain, RV free wall, strain, FAC degree of RV, RVOT Systolic excursion, PAP and TDI degree after six months of treatment.

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**تأثير استخدام عقار داباجليفلوزين على وظيفة البطين الأيمن للقلب
والتي تم تقييمها بواسطة المعاملات المختلفة للموجات الفوق صوتية للقلب
لدى مرضى فشل القلب مع الكسر القذفي المحفوظ**

يُمثل فشل القلب مع الكسر القذفي المحفوظ حوالي ٥٠٪ من المرضى الذين يعانون من فشل القلب. ورغم أن البطين الأيمن كان مهملاً في السابق، فقد برز بشكل مهم في السنوات الأخيرة. حيث يُمثل اضطراب البطين الأيمن ٤٪ - ٥٠٪ من المرضى الذين يعانون من فشل القلب مع الكسر القذفي المحفوظ.

يتم استخدام الداباجليفلوزين في المرضى الذين يعانون من فشل القلب مع انخفاض الكسر القذفي سواء في وجود أو عدم وجود داء السكري من النوع الثاني.

وقد أُجريت هذه الدراسة لتقييم تأثير الداباجليفلوزين على وظيفة البطين الأيمن باستخدام المعاملات المختلفة للموجات الفوق صوتية للقلب.

وقد شملت هذه الدراسة ٤٠ مريضاً من مرضى فشل القلب مع الكسر القذفي المحفوظ من مرضى مستشفى جامعة العريش.

وقد أظهرت هذه الدراسة أن الداباجليفلوزين يحسن خصائص ووظيفة البطين الأيمن للقلب في المرضى الذين يعانون من فشل القلب مع الكسر القذفي المحفوظ.