REVIEW ARTICLE

Effect of adding SGLT2 Inhibitors and Site of Right Ventricular (RV) Pacing on Left Ventricular (LV) Dyssynchrony, Contraction Efficiency and RV Function

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ABSTRACT
SGLT2 inhibitors have become cornerstones in the treatment of HF across the spectrum of ejection fractions, with several trials such as EMPEROR-Preserved and DELIVER showing these drugs to decrease all-cause mortality and hospitalizations. Whereas the favorable effects of SGLT2i on left ventricular function are well established, those of SGLT2i on right ventricular function remain relatively unexplored. This review shall investigate the importance of RV function in HF, particularly about the positioning of the pacemaker lead and its impact on cardiac output. It was underlined that the most important function of advanced echocardiographic techniques, such as three-dimensional echocardiography and speckle-tracking imaging, provided an opportunity for more valid RV systolic function compared to traditional measures such as TAPSE. This includes the following: SGLT2i probably may improve RV function due to the drug's effect of reduction in pulmonary arterial stiffness, hemodynamic profile improvement, and favorable metabolic shift in myocardial energy utilization. Several emerging pieces of evidence suggest that, beyond the reductions in hospitalization, SGLT2i is associated with significant improvements in RV systolic function, as evidenced by improved parameters such as RV fractional area change and longitudinal strain. Further mechanistic studies, focusing on the action of SGLT2i on RV function, should be emphasized, including anti-inflammatory effects and vascular compliance. In brief, the incorporation of SGLT2i in heart failure management may exert an optimum effect on both LV and RV functions with a strong emphasis on overall cardiac evaluation. This work will also require extended comprehension of RV dynamics in the clinical field toward better improvement in the outcomes among patients suffering from heart failure through targeted therapies.

Keywords: SGLT2 inhibitors, Contraction Efficiency, pacing strategies, Right Ventricular Pacing, Left Ventricular (LV) Dyssynchrony, RV Function.
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INTRODUCTION

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have emerged as a fundamental therapy for heart failure (HF) across the spectrum of ejection fractions. Recent results from the EMPEROR-Preserved and the DELIVER randomized trials have shown that SGLT2i (empagliflozin and dapagliflozin, respectively) can reduce all-cause mortality and hospitalizations due to HF in patients with HF with a mildly reduced or preserved ejection fraction. The guidelines for the treatment of patients with heart failure with a reduced ejection fraction (HFrEF) by the European Society of Cardiology from September 2021 set SGLT2i as a pillar therapy with an IA class recommendation based on the results of the EMPEROR-Reduced and DAPA-HF trials. **(Pabel et al., 2020)** The beneficial effects of SGLT2i on the left ventricular systolic and diastolic function, circulating natriuretic peptide levels, and functional symptom burden have been demonstrated in several studies, but not much is known about the effects of these drugs on the right ventricular (RV) systolic function. The RV is often neglected because of its complex anatomy and the difficulty of obtaining satisfactory imaging “windows” in daily practice. However, the RV has been shown to play an important prognostic role following cardiac surgery and in patients with HF, pulmonary arterial hypertension, or ischemic heart disease. In clinical practice, the assessment of the RV function is usually undertaken by measuring only the longitudinal systolic function, as reflected in the measurement of the tricuspid annular plane systolic excursion (TAPSE) and tricuspid lateral annular systolic

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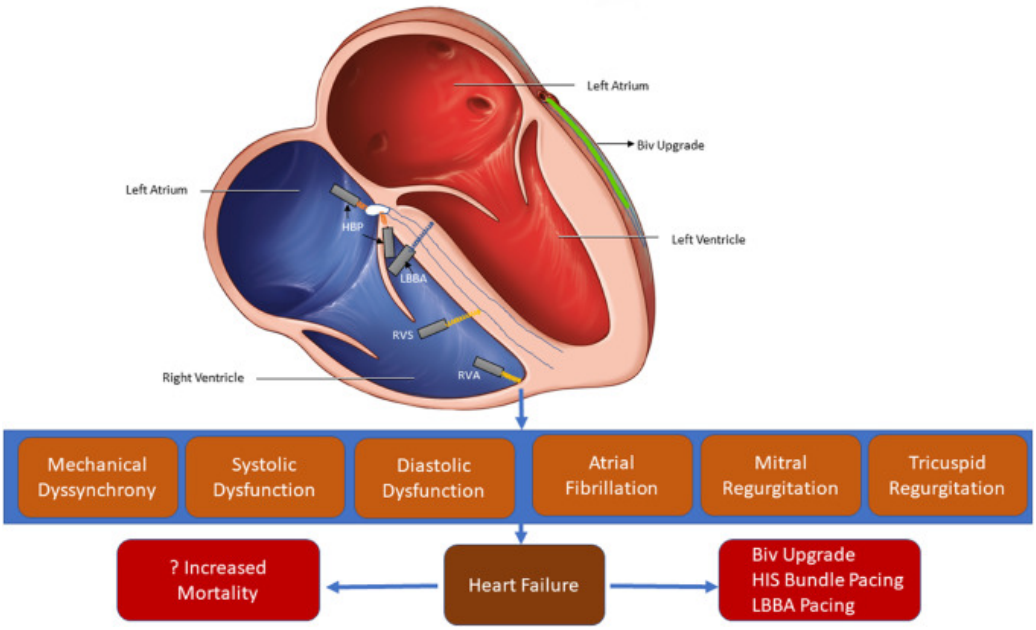

*Adverse effects of right ventricular pacing on cardiac function: prevalence, prevention and treatment with physiologic pacing***(Brown et al., 2021)**

velocity (s' wave) derived from Doppler tissue imaging. **(Dimitriadis et al., 2023)**

Pacemakers

Pacemakers are small devices implanted in the chest to help regulate heartbeats. They are used to treat conditions like bradycardia, where the heart beats too slowly. The device sends electrical signals to prompt the heart to beat at a normal rate. **(Dimitriadis et al., 2023)**

Key Components:

Pulse Generator: Contains the battery and electronic circuitry.

Lead Wires: Connect the generator to the heart, delivering electrical impulses.

Types:

Single-chamber: Monitors and paces one chamber of the heart.

Dual-chamber: Paces two chambers, coordinating atrial and ventricular activity.

Biventricular: Used in cardiac resynchronization therapy to improve heart function in heart failure patients.

RV Apical lead position vs septal position pacing and its effect on LV function:

The position of the right ventricular (RV) lead in pacemaker implantation can significantly impact left ventricular (LV) function, particularly in patients with heart failure or those requiring cardiac resynchronization therapy. **(Dimitriadis et al., 2023)**

RV Apical Lead Position

Location: The lead is positioned at the apex of the right ventricle.

Effects:

Contraction: This position can lead to asynchronous contraction of the ventricles, particularly in patients with left bundle branch block (LBBB).

Potential Downsides: Studies have shown that apical pacing can result in worse LV function over time, potentially leading to ventricular remodeling and worsening heart failure symptoms.

RV Septal Lead Position

Location: The lead is positioned in the interventricular septum.

Effects:

Contraction: Septal pacing tends to synchronize the contractions of the left and right ventricles more effectively.

Improved Function: This positioning is associated with better LV function, improved cardiac output, and reduced heart failure symptoms compared to apical pacing.

Cardiac Resynchronization Therapy (CRT): In CRT, biventricular pacing (with leads in both ventricles) often employs septal pacing to optimize synchrony.

LV Function: Septal pacing is generally preferred for enhancing LV function, especially in patients with conduction abnormalities. It can lead to improved outcomes in heart failure management.

Patient Selection: The choice of pacing lead position should consider individual patient anatomy, underlying heart conditions, and specific therapeutic goals. **(Dimitriadis et al., 2023)**

SGLT2i and its role in LV function

SGLT2 inhibitors (SGLT2i) are a class of medications primarily used to manage type 2 diabetes, but they have also shown significant benefits in heart failure and in improving left ventricular (LV) function. Here's how they work and their impact on LV function: **(Fernandez et al., 2021)**

Mechanism of Action

Glucose Reabsorption: SGLT2 inhibitors block the sodium-glucose cotransporter 2 (SGLT2) in the kidneys, reducing glucose reabsorption and promoting its excretion in urine. This leads to lower blood glucose levels.

Diuretic Effect: They also have a mild diuretic effect, which can help reduce fluid overload in heart failure patients.

Impact on LV Function

Heart Failure Benefits:

SGLT2 inhibitors have been shown to reduce hospitalizations for heart failure and improve clinical outcomes in patients with both diabetes and heart failure, including those with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF).

Cardioprotective Effects:

Improved Hemodynamics: The reduction in volume overload helps improve cardiac output and reduces the workload on the heart.

Myocardial Energy Metabolism: They may enhance myocardial efficiency by shifting the heart's energy substrate utilization from glucose to ketones, which can be more efficient.

Anti-inflammatory Effects: SGLT2 inhibitors may reduce inflammation and fibrosis in cardiac tissue, promoting better LV function.

Improved LV Ejection Fraction:

Studies have indicated that SGLT2 inhibitors can lead to improvements in LV ejection fraction, particularly in patients with heart failure, thereby enhancing overall cardiac function.

Clinical Implications

Guideline Recommendations: Due to their positive effects on heart failure outcomes, SGLT2 inhibitors are recommended as part of the standard therapy for heart failure patients, regardless of diabetes status.

Individualized Treatment: The decision to use SGLT2 inhibitors should consider the patient's overall health, comorbidities, and specific heart failure characteristics. **(Fernandez et al., 2021)**

Impact on RV function

The fractional area change (FAC), on the other hand, gives us an insight into the radial contraction of the RV. Because these parameters are load- and angle-dependent, advanced echocardiographic methods, such as speckle-tracking echocardiography (STE) measuring the longitudinal strain of the RV free wall (RV FWS) and the three-dimensional RV ejection fraction (3D RVEF), have recently emerged as more accurate estimates of the RV systolic function. The measurement of the 3D RVEF overcomes the limitations of the geometric assumption of the RV and integrates both the longitudinal and radial components of the myocardial muscle contraction, whereas TAPSE and s' wave measure only the longitudinal RV function in the basal region of the RV free wall. **(Martins et al., 2021)**

The 3D echocardiography assessment of the RV ejection fraction and RV FWS have been shown to be comparable to the gold standard cardiac magnetic resonance (CMR) and were shown to be an independent predictor of cardiac death and major adverse cardiovascular events (MACE) in patients with diverse cardiovascular diseases. Furthermore, the ratio between the TAPSE and systolic pulmonary artery pressure (SPAP) represents the non-invasive measurement of the right ventriculo-arterial coupling and the RV contractile function. **(Trum et al., 2021)**

The exact effects of SGLT2i on the RV function have not been thus far studied in great detail. Patoulias and colleagues emphasized the need to evaluate the effects of SGLT2i on the RV function, citing the RV as a "forgotten" cardiac chamber with significant knowledge gaps. A post hoc analysis of the EMPA-HEART CardioLink-6 trial in patients with type II diabetes mellitus and coronary artery disease (CAD) showed no differences in the RV mass index, RV volume, and RV EF, measured by CMR after 6 months of empagliflozin compared with placebo. **(Sauer et al., 2024)**

Conversely to this, a recent retrospective study demonstrated a significant improvement in the pulmonary artery's stiffness and RV systolic function in HFrEF patients after 6 months of SGLT2i therapy compared to the baseline, as measured by TAPSE, s' wave, and FAC, along with a significant decrease in the mean pulmonary systolic pressure. However, to the best of our knowledge, our study is the first one that prospectively examined the effects of an SGLT2i addition to OMT in HFrEF outpatients on the RV systolic function using advanced 3D echocardiography and 2D speckle-tracking of the RV free wall. **(Fernandez et al., 2021)**

Mouton and colleagues emphasized a cut-off value of RV FWS $< -16\%$ for the diagnosis of the RV systolic dysfunction with a high specificity and moderate sensitivity for poor outcomes in the HFrEF population. 4 times fewer patients in the OMT+SGLT2i group had RV FWS $\leq -16\%$ than patients only receiving OMT alone. Moreover, RV FWS is not only a prognostic parameter but is also able to detect the subtle deterioration of the RV systolic function despite the preserved TAPSE, s' wave, and FAC in HF patients . Another important feature of RV FWS is that it likely reflects the extent of RV myocardial fibrosis in the later stages of HFrEF development . These observations are important in the context of our results, as our study showed a numerical improvement in all the measured parameters of the RV systolic function from the baseline to the 3mFU in patients receiving SGLT2i in addition to OMT, however, RV FWS was the only echocardiographic indicator that was statistically significant improved compared to the OMT-only group. **(Lam-Chung, 2023)**

The exact pathophysiological mechanisms explaining these results wait to be elucidated. However, the beneficial role of SGLT2i in reducing the extent of pulmonary hypertension and RV remodeling can be explained by their multifactorial and pleiotropic effects. SGLT2i have metabolic, vascular, and hemodynamic effects. They reduce body weight due to renal caloric loss by glycosuria, have beneficial effects on cardiac metabolism, and improve cardiac energetics. They also reduce myocardial oxidative stress, and by inhibiting the myocardial sodium-hydrogen exchanger 1 (NHE1), they reduce cytoplasmic sodium and calcium levels. **(Subramanian et al., 2023)**

The combination of the different mechanisms prevents cardiac remodeling. Due to the mechanism of osmotic diuresis, the initial volume depletion results in a decrease in the pulmonary pressure within the first few days after the initiation of the treatment. The patients in the study did

not differ in terms of the average diuretic dose, so the possible explanation for the SGLT2i effect is the addition of the osmotic diuretic and natriuretic effects, which led to a reduction in the RV preload. In addition, SGLT2 inhibitors attenuate the activation of the renin-angiotensin-aldosterone system (RAAS) and reduce the discharge of the sympathetic nervous system, which in turn attenuates systemic and pulmonary arterial stiffening. The beneficial role of SGLT2i in reducing pulmonary arterial stiffness (PAS) wherefore patients exhibit better pulmonary vascular compliance, which attenuates the RV afterload and thus improves the RV systolic function. **(Forrester et al., 2024)**

Additionally, the previously demonstrated reduction in the LV filling pressure and improvement in the LV diastolic function is reflected in the improvement in the RV function. Another beneficial effect of SGLT2i that may explain the improvement in the RV is its action on vascular cells through an anti-inflammatory and antioxidant effect, also increasing the angiogenesis and nitric oxide bioavailability from the endothelium, leading to pulmonary and systemic vasodilation, thereby reducing the RV preload and afterload. **(Ellison, 2021)**

Sodium-glucose cotransporter type 2 inhibitors (SGLT2i) act by preventing sodium and glucose reabsorption from the kidney's proximal tubules. This process indirectly influences many pathways, resulting in a variety of consequences in the body, including decreased vascular inflammation, generation of reactive oxygen species, and improved endothelial function via lowering vascular stiffness. Randomized controlled studies have been conducted in recent years to investigate the impact of SGLT2i in HF patients. These studies found that SGLT2i lowers cardiovascular mortality, all-cause mortality, and hospitalization in HF patients with and without diabetes. On the other hand, few studies examined the effects of SGLT2i on RV function. Although some research shows that SGLT2i have a favorable effect on RV functioning, other studies did not show substantial findings. **(Vallon & Verma, 2021)**

SGLT2i exert their beneficial effects through various mechanisms. Multiple pleiotropic mechanisms beyond glycemic control are thought to be responsible for the benefits of SLGT2 inhibitors in HF. The benefits encompass natriuresis and a decrease in plasma volume, enhanced oxygen-carrying capability, and improved supply of oxygen to tissues due to an elevation in hematocrit. Possessing robust antioxidant and anti-inflammatory characteristics, they enhance endothelium-dependent vasodilation by increasing the bioavailability of nitric oxide produced by the endothelium. They also show their positive effects by decreasing glomerular pressure and oxygen consumption in the proximal tubules of the kidneys, modulating Na+/H+ exchange in the heart and kidneys, and adipokine production. **(Hämäläinen, 2024)**

SGLT2i induces a significant shift in myocardial metabolism, transitioning from reliance on glucose to usage of fatty acids, ketone bodies, and branched-chain amino acids. This shift results in the augmentation of myocardial energy. An alternative hypothesis suggests that in individuals with diabetes, SGLT2i in the proximal tubule may favorably affect the heart via a steep Frank-Starling curve driven by natriuresis and glycosuria. Each beneficial SGLT2i effect can be considered as a mechanism that contributed to the improvement of RV function shown in our meta-analysis. **(Aalen, 2021)**

SGLT2i has been shown to provide a significant improvement in pulmonary artery stiffness (PAS) and RV systolic function compared to baseline as measured by TAPSE and FAC in HF patients. Another study in HF patients with the CardioMEMS pulmonary artery pressure (PA) sensor showed that empagliflozin caused rapid decreases in PA pressures, independent of loop diuretic administration. mechanisms beyond the diuretic effect of the SGLT2i in HF contribute to the observed reductions in PA pressures. SGLT2i may lower PA pressures by positively impacting endothelial functions, primarily through their vasodilator effect on nitric oxide. **(Aalen, 2021)**

In addition, the initial volume reduction by the effect of osmotic diuresis causes a decrease in lung pressure. Elevated PA pressures are indicative of impending HF symptoms, unplanned hospital admissions, and increased mortality SGLT2i resulted in positive changes in RV function and sPAS, as well as symptomatic and functional well-being. Reducing PAS provides better pulmonary vascular compliance, alleviates RV afterload, and ultimately improves RV systolic function. In addition, the previously demonstrated reduction in LV filling pressure and improvement in diastolic function caused by SGLT2i may also be considered to contribute to the improvement in RV function. The addition of SGLT2i to optimal medical therapy significantly reduces the degree of tricuspid regurgitation compared to optimal medical treatment alone. **(Akhtar et al., 2023)**

Effects of long-term RV pacing. In patients with drug-refractory AF, ablation of the AV node and permanent pacing have proven to be effective. However, the beneficial effect of the therapy may (partially) be reversed by the non-physiologic activation pattern of the interventricular septum. Several studies have reported the negative effects of permanent RV pacing. Regional perfusion defects, asymmetrical hypertrophy of the ventricular wall, and impairment of LV ejection fraction have been reported after permanent RV pacing. Furthermore, the induction of LV desynchrony after long-term RV pacing in 23 patients with congenital complete AV block. Following long-term RV pacing, the mean SPWMD, as a measure of LV desynchrony, had significantly increased as compared to baseline. **(Meyer et al., 2023)**

In addition, the septal-to-lateral delay as measured by TDI was significantly larger in patients with permanent pacing as compared with control patients (59 18 ms vs. 19 9 ms, p 0.01). Similar results were demonstrated in the current study, showing an increase in SPWMD from 63 31 ms to 121 64 ms (p 0.05) after long-term RV pacing, and in 27 (49%) patients the SPWMD exceeded 130 ms, indicating substantial LV desynchrony. The presence of LV desynchrony may result in systolic LV dysfunction

(21,22). A significantly lower cardiac output in patients with LV desynchrony after long-term RV pacing as compared with healthy volunteers. In addition, LV end-diastolic diameter had significantly increased in these patients as compared with volunteers (5.5 0.7 cm vs. 4.6 0.6 cm, p 0.05). The observations in the present study are in line with these previous results: patients with LV desynchrony after long-term RV pacing showed a decrease in LV ejection fraction, with an increase in LV volumes and LV end-diastolic diameter indicating LV dilatation. **(Prosperi et al., 2023)**

Assessment of LV desynchrony. LV desynchrony was measured by M-mode echocardiography. With M-mode echocardiography, the SPWMD can be measured. The SPWMD indicates the delay between the maximal systolic motion of the septum and the LV free wall, reflecting intraventricular desynchrony. At baseline, none of the patients in the current study had SPWMD exceeding 130 ms, which is used as the upper limit of normal LV synchrony. After long-term RV pacing, however, 27 patients (49%) had developed LV desynchrony, as illustrated by a SPWMD 130 ms. In addition to SPWMD, TDI was used to assess the septal-to-lateral delay. **(Sabbah et al., 2023)**

Tissue Doppler imaging is a sophisticated echocardiographic technique that permits the measurement and timing of myocardial systolic (and diastolic) velocities. By comparing the differences in time to peak systolic velocities of different LV regions, TDI can identify LV desynchrony. Both M-mode using SPWMD and TDI using the septal-to-lateral delay have proven to be effective in the detection of LV desynchrony. In the current study, a good agreement was detected between the SPWMD and septal-to-lateral delay. In particular, all patients with LV desynchrony on M-mode also exhibited LV desynchrony on TDI, and only 4 patients (8%) without LV desynchrony on M-mode had LV desynchrony on TDI, indicating minimal underestimation of LV desynchrony by SPWMD. substantial underestimation of LV desynchrony by M-mode echocardiography as compared to TDI in patients with severe LV dysfunction. **(Das, 2024)**

In particular, in patients with ischemic LV dysfunction and akinesia of the (Antero-) septum, assessment of SPWMD may not be feasible and TDI may be preferred for accurate detection of LV desynchrony. however, all patients had preserved LV function without significant valvular disease, explaining the better agreement between the 2 techniques. Clinical implications. The observations in the current study demonstrate that RV pacing may induce LV desynchrony in a substantial percentage of patients with preserved LV function who undergo AV node ablation. In addition, the induction of LV desynchrony was associated with a deterioration of LV function and clinical status. Therefore, it needs to be considered whether these patients should have undergone biventricular pacing rather than RV pacing. **(Green, 2021)**

Recently, several studies have compared different pacing strategies for patients with AF treated with AV node ablation and permanent pacing. In the PAVE (Post AV nodal ablation Evaluation) trial, 184 patients treated with AV node ablation and pacemaker implantation were randomly assigned to RV pacing or biventricular pacing. **(Vallon & Verma, 2021)**

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