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Mini Review

The Effects and the Mechanisms of Sodium Glucose Cotransporter-2 Inhibition in Heart Failure

Lei zhou and Hui Gong*

Department of Cardiology, Jinshan Hospital of Fudan University, Shanghai, 201508, China

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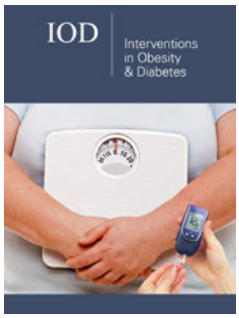

***Corresponding author:** Hui Gong, Department of Cardiology, Jinshan Hospital of Fudan University, 1508 Longhang Road, Jinshan District, Shanghai, 201508, China, E-mail address: 13918566212@163.com (H Gong)

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Abstract

Although treatments are currently established, heart failure (HF) remains the leading cause of hospitalization and mortality worldwide. Therefore, new therapeutic targets are needed to improve the prognosis of patients with heart failure, especially those with preserved ejection fraction. In recent years, many clinical studies have shown that sodium glucose cotransporter-2inhibitors can significantly reduce the hospitalization rate and mortality of heart failure. It is expected to become a new method for the treatment of heart failure, and this effect also exists in non-diabetic heart failure patients. But its potential mechanisms of action are not fully understood yet and needs further exploration. This article reviews the effects and the potential mechanisms of SGLT2 inhibitors in heart failure.

Keywords: SGLT2 inhibitors; Heart failure

Introduction

Individuals with diabetes are not only with high risk of developing heart failure but also with increased risk of death [1]. Different types of hypoglycemic drugs have different cardiovascular safety, so it is necessary to evaluate the cardiovascular safety of new hypoglycemic drugs. In recent years, many large-scale randomized controlled trials on SGLT2 inhibitors for oral hypoglycemic agents such as (EMPA-REG OUTCOME (The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Trial); CANVAS Program (The Canagliflozin Cardiovascular Assessment Study Program); DEGLARE-TIMI 58 (The Dapagliflozin Effect on Cardiovascular Events -TIMI 58 Trial); DEFINE-HF Trial (The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial) have shown that SGLT2 inhibitors could significantly reduce the hospitalization rate and the composite endpoint of cardiovascular mortality in patients with heart failure compared to the placebo group [2-5]. This effect persisted even in non-diabetic patients. The mechanisms responsible for the cardioprotective effects of SGLT2 inhibitors remain uncertain. This article summarizes the possible mechanisms of SGLT2 inhibitors in heart failure as follows.

The Biological Role of SGLT2

Sodium-glucose co-transporters (SGLTs) belong to the SLC5 family of active glucose transporters with 12 members. Within the family, SGLT1 and SGLT2 have received the most attention in medicine. SGLT-1 is mainly expressed on the brush-border membrane of the small intestine and the straight (S3 segment) renal proximal tubule, whereas SGLT-2 is mainly expressed on the apical membrane of renal proximal convoluted tubules (S1 and S2 segments) [6]. SGLT2 is a low-affinity, high-capacity glucose transporter that accounts for about 90% of the reabsorption of filtered glucose by the kidney, and the remaining 10% is completed by SGLT-1 [7,8]. In contrast to traditional hypoglycemic drugs, SGLT2 inhibitors lower plasma glucose levels through competitively binding to sodium glucose cotransporter-2 in the kidney, thereby reducing the reabsorption of glucose and sodium by the kidney. As a result, it can produce a range of beneficial systemic effects, including reduced blood glucose levels, lower blood pressure, sodium diuresis, osmotic diuresis, renal and cardiac protection [9].

The Mechanism of SGLT2 Inhibitor in Heart Failure

SGLT2 inhibitor improves myocardial metabolic remodeling

Substrates for normal cardiac energy metabolism include fatty acids and sugars, lactic acid, branched chain amino acids, and ketone bodies, with fatty acid oxidation as the main substrate. During heart failure, due to myocardial hypoxia, the heart undergoes metabolic

remodeling, and myocardial fatty acid oxidation is significantly reduced. Myocardial substrate oxidation switches from fat to carbohydrate oxidation (fetal-like metabolism) [10]. Accumulating reports have demonstrated that SGLT-2 inhibitors could promote the degradation of fatty acids, glucose, branched-chain amino acids, and ketone bodies during heart failure, resulting in improved myocardial energetics and efficiency. Santos-Gallego et al. found that the SGLT2 inhibitors empagliflozin could increase the oxidation of ketone bodies, branched chain amino acids, fatty acids and related metabolic enzymes expression in the myocardium in a heart failure pig model, thereby improving myocardial energy metabolism and enhancing ventricular systolic function and ameliorating adverse left ventricular remodeling [11]. In the mouse model of diabetes, the SGLT2 inhibitor empagliflozin has been shown to increase the total cardiac ATP production by 30% through increasing the oxidation rate of glucose and fatty acids [12]. Yurista et al. [13] reported that SGLT-2 inhibitor empagliflozin improved cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction through increasing the oxidation of ketone bodies [13]. It has been shown that a single dose of empagliflozin enhanced cardiac energy status by increasing plasma ketone levels [14].

SGLT2 inhibitor improves myocardial remodeling

Ventricular remodeling is the basic pathophysiological process of the occurrence and development of heart failure. Several studies have demonstrated that SGLT2 inhibitors could alleviate ventricular remodeling. Zhang et al. reported that SGLT2 inhibitors dapagliflozin could reverse the left ventricle's concentric remodeling by reducing aortic sympathetic tone activity and aortic inflammation in a pig model of heart failure with preserved ejection fraction [15]. Myocardial fibrosis is also an important pathological feature of myocardial remodeling. It has been shown that the SGLT2 inhibitors empagliflozin could attenuate myocardial fibrosis and ventricular remodeling by inhibiting transforming growth factor β/Smad signaling pathway in a mouse model of diabetes [16], Lee et al. [17] showed that in infarcted rat hearts, the SGLT2 inhibitors dapagliflozin promoted the differentiation of macrophages into M2 anti-inflammatory types by inhibiting the STAT3 signaling pathway, while M2 macrophages inhibit fibroblasts toward myofibroblast cell differentiation to reduce myocardial fibrosis [17]. Myocardial fibrosis that was observed in obese and type 2 diabetic mice was alleviated after empagliflozin treatment through reducing cardiac macrophage infiltration [18]. Moreover, empagliflozin has been shown to exhibit improved atrial and ventricular remodeling in hypertensive heart failure rats [19].

SGLT2 inhibitor improves sympathetic nerve activity

Excessive activation of the sympathetic nervous system (SNS) plays an important role in the occurrence and development of heart failure, leading to an increase in cardiac load and atrial/ventricular remodeling. Studies have shown that the use of SGLT2 inhibitors could reduce aortic blood pressure without causing compensatory changes in heart rate. Therefore, it was speculated that SGlT2 inhibitors might improve heart failure by generating sympathetic inhibitory effects [20], Kiuchi et al. [21] reported that long-term use of the SGLT2 inhibitor empagliflozin ameliorated cardiac sympathetic nerve activity in a patient with heart failure [21]. In a pig model of heart failure with preserved ejection fraction, the aortic sympathetic nerve activity was attenuated after dapagliflozin treatment through downregulating the expression of tyrosine hydroxylase in the aorta [15].

SGLT2 inhibitors regulate calcium homeostasis in cardiomyocytes

SERCA2a is a calcium ion ATPase on the sarcoplasmic network of cardiomyocytes. Its activity is regulated by phospholamban. During the diastole of cardiomyocytes, it can excrete calcium ions from the cytoplasm into the sarcoplasmic network to promote myocardial relaxation. In cardiomyocytes of heart failure, SERCA2a activity is significantly reduced, accompanied by Ca^{2+} transport disorder, which is manifested by diastolic sarcoplasmic reticulum intake of Ca^{2+} and accumulation of intracellular Ca^{2+}, which affects the diastolic function of the heart; while systolic calcium release decreases , Ca^{2+} decreases in cytoplasm, and systolic function decreases accordingly [22,23]. It has been shown that empagliflozin improved LV diastolic function by increasing sarcoplasmic endoplasmic reticulum Ca^{2+} -ATPase (SERCA2a) activity in genetic diabetic mice [24]. Joubert et al. [25] also found that dapagliflozin enhanced SERCA2a activity leading to improved cardiac contractile dysfunction in a diabetic lipodystrophic mouse model [25].

SGLT2 inhibitor improves tissue cell hypoxia

Tissue cells are often hypoxic during heart failure. Studies have found that SGLT2 inhibitor empagliflozin could increase the concentration of erythropoietin and hematocrit in plasma, promote the production of red blood cells and hemoglobin, improve tissue hypoxia, and ameliorate heart failure [26]. A COX regression analysis of a large randomized controlled clinical trial of englitazone also showed that hematocrit and increased hemoglobin may be the main reasons for mediating the cardiovascular effects of empagliflozin [27]. Therefore, SGLT2 inhibitors may improve heart failure by increasing oxygen supply to tissue cells throughout the body.

SGLT2 inhibitors inhibit the activity of the sodium-hydrogen exchanger NHE

Sodium hydrogen exchange protein (NHE) is responsible for the exchange of sodium ions and hydrogen ions on the cell membrane to maintain the electrolyte distribution. NHE is involved in the occurrence and development of heart failure and myocardial hypertrophy, and inhibition of NHE activity can prevent and ameliorate heart failure [28,29]. Studies have observed that the SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin could inhibit the activity of NHE, reduce the sodium and calcium concentrations in the cytoplasm of myocardial cells, and increase

the calcium ion concentration in mitochondria [30,31]. Therefore, some scholars speculated that SGLT2 inhibitors might ameliorate heart failure by inhibiting the activity of NHE to regulate the ion imbalance of myocardial cells during heart failure.

SGLT2 inhibitors reduce cardiac preload and afterload

Myocardial cells are often hypoxic during heart failure. The oxygen consumption of cardiomyocytes is related to cardiac workload and heart rate. The SGLT2 inhibitors reduce preload through sodium diuresis and osmotic diuresis [32]. SGLT2 inhibitors reduce blood pressure and arterial stiffness without increasing heart rate, thereby decreasing cardiac afterload [33]. Several studies have revealed that SGLT-2 inhibitors (dapagliflozin; canagliflozin empagliflozin) could lead to a considerate reduction in arterial stiffness in T2DM patients [34-36]. This effect has been attributed to improved endothelial dysfunction [15,36]. It was hypothesized that the sustained reduction in intravascular volume and blood pressure may lead to a reduction in cardiac preload and afterload, respectively, thereby alleviating cardiac workload and improving cardiac function [32].

SGLT2 inhibitor improves arterial stiffness and endothelial cell function

Several researches have reported significant reduction in arterial stiffness in patients with T2DM treated with empagliflozin, canagliflozin, and dapagliflozin. This effect was related to the improvement of endothelial dysfunction by SGLT2 inhibitors. Reduced arterial stiffness and improved endothelial function could lead to decreased blood pressure, reduce cardiac load, improve myocardial cell hypoxia, and ameliorate heart failure [15,34-36]. In addition, Zhang et al. [15] found that the SGLT2 inhibitor dapagliflozin improved endothelial cell function by upregulating the NO-cGMP-PKG signaling pathway and inhibiting the inflammatory response of endothelial cells.

Conclusion

Current clinical trial studies of SGLT-2 inhibitors demonstrate beneficial effects on heart failure in non-diabetic patients. A clinical trial of the SGLT2 inhibitor dapagliflozin included 4,744 patients with chronic heart failure and reduced ejection fraction (EF<45%). Diabetes was neither an inclusion nor exclusion criterion in this study. After 1.5 years of treatment and follow-up, the study indicated that the SGLT2 inhibitor dagliflozin reduced the risk of exacerbating heart failure by 30% and the risk of cardiovascular death by 18% compared to the placebo group [5]. In summary, SGLT2 inhibitors are expected to become a new class of drugs for treating heart failure. The beneficial effects of SGLT2 inhibitors on heart failure maybe by improving ventricular remodeling, improving myocardial metabolic remodeling, reducing autonomic nerve activity, improving myocardial cell calcium homeostasis, inhibiting NHE activity and so on. But a large number of basic and clinical trials are still needed to prove the feasibility of SGLT2 inhibitors in the treatment of heart failure. In the future, SGLT-2 inhibitors may be used to treat heart failure in patients with non-type 2 diabetes.

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