

Research progress of sodium-glucose cotransporter 2 inhibitors and autonomic nervous function in patients with heart failure

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Abstract: Heart failure (HF) seriously affects human health, and the autonomic nervous system disorder is an important basis for the occurrence and development of heart failure. Sodium-glucose cotransporter 2 inhibitor (SGLT2i) was originally used to treat diabetes. Basic and clinical studies have reported that SGLT2i is effective in reducing the incidence of heart failure, hospitalization, and all-cause mortality in patients with or without diabetes mellitus. Because of its significant cardiovascular benefits, SGLT2i has been used as a guideline in the treatment of heart failure. The mechanisms by which SGLT2i improves heart failure include regulation of volume, cardio-renal mechanism, metabolic action, improvement of myocardial remodeling, reduction of inflammation and oxidative stress. Recent studies have found that SGLT2i is closely related to autonomic nervous function, and may be a new mechanism to improve heart failure. This article focuses on discussing the benefits of SGLT2i on heart failure and its effects on autonomic nervous system, providing a new basis for clinical treatment of heart failure.

1. Introduction

Heart failure (HF), referred to as heart failure, is a group of clinical syndroms with pulmonary circulation and/or systemic circulation congestion as the main manifestation. The cardiac output caused by various cardiovascular diseases can not meet the metabolic needs of body tissues, and is also the most serious stage of various cardiovascular diseases^[1]. According to statistics^[2], the prevalence of heart failure in the United States is about 3.5%, there are about 6.5 million cases of heart failure patients, the incidence of male 50-59 years old is 8/1 000,80 years old increased to about 66/1 000. Projections estimate that by 2030, more than 8 million people over the age of 18 will be affected by heart failure. The incidence of clinical chronic heart failure is on the rise year by year, becoming one of the major diseases that seriously affect human health. Sodium-glucose cotransporter inhibitor 2 (SGLT2i) is a new type of hypoglycemic drug, which reduces glucose reabsorption by inhibiting the activity of sodium - glucose cotransporter 2 protein in proximal convoluted renal tubules. And thus play a role in lowering blood glucose. At present, more and more experiments have confirmed its efficacy and benefits in patients with heart failure, and it has been included in the

guidelines for heart failure management at home and abroad. Combined with traditional angiotensin converting enzyme inhibitors, β -blockers and aldosterone antagonists, "Golden Triangle" anti-heart failure drugs have become a "new quadruple" drug for the treatment of heart failure^[3]. This paper summarized the recent studies on the effects of SGLT2 inhibitors on HF patients, discussed the current status of the studies on the effects of SGLT2 inhibitors on HF patients, analyzed the possible potential mechanism of the effects of SGLT2 inhibitors on autonomic nervous system, and provided evidence and reference for the treatment of SGLT2 inhibitors on HF patients in China.

2. Heart failure and autonomic nervous system

Overactivation of the Sympathetic Nervous System (SNS) plays a crucial role in the occurrence and development of heart failure and is closely related to the deterioration of heart failure patients^[4]. In the early stage of heart failure, the activation of SNS is beneficial to the compensation and maintenance of heart function. However, the disorders of hemodynamics and neurohumoral factors begin to appear along with the development of heart failure, such as the continuous increase of SNS excitability, the increase of humoral factors such as aldosterone and angiotensin II, which eventually lead to water and sodium retention, myocardial remodeling and decompensated heart failure. In heart failure, atrial receptors and arterial pressure receptors reflexively cause enhanced sympathetic nerve excitability. Adrenal medulla, and sympathetic nerve endings release a large amount of adrenaline and norepinephrine into the blood, and plasma catecholamine (CA) level is significantly increased, speeds up the heart rate, changes the rhythm of the heart, increases the cardiac load, Direct cardiotoxic effects such. As down-regulating the number of β -adrenergic receptors and up-regulating β -inhibitory protein and β -adrenergic receptor kinase further worsen cardiac function, and the deterioration of cardiac function forms a vicious cycle with the activation of sympathetic nervous system^[5].

3. Related studies on the cardiovascular benefits of SGLT2i

As early as 2015, Bernard Zinman et al. ^[6] first identified the protective effect of englt2I on cardiovascular disease. A total of 7020 patients with diabetes (median observation period of 3.1 years) were enrolled in the englt2I group, which showed significantly lower rates of cardiovascular mortality and hospitalization for heart failure compared with the placebo group. In 2019, John J V McMurray et al. [7]found that among patients with heart failure with reduced ejection fraction, the risk of worsening heart failure and cardiovascular death was lower in patients receiving daglipzin than in those receiving placebo, regardless of whether they had diabetes. The EMPUSLE trial (The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial) showed that, compared with placebo, englagliflozin in patients hospitalized for acute heart failure resulted in significant clinical benefits over 90 days, including reduced mortality, improved quality of life, weight loss, and good safety profile. In a subsequent large randomized controlled study in 2022, Scott D Solomon et al. [8] enrolled 6263 patients with a mean follow-up of 2.3 years, and the incidence of cardiovascular death was 7.4% and 8.3% in the daglipzin and placebo groups, respectively. The benefit of SGLT2i was further demonstrated in both mildly reduced ejection fraction and FRF-preserved heart failure. A series of studies on the cardiovascular benefits of SGLT2i have pushed this drug into the hot spot in the treatment of heart failure.

4. Study on the effect of SGLT2i on the autonomic nervous system

In people with type 2 diabetes, high blood sugar and insulin levels often overexcite SNS, which can lead to increased incidence of heart failure and other cardiovascular diseases. However, Motoaki Sano et al. [9] found no significant increase in heart rate in patients treated with SGLT2i, suggesting

that SGLT2 inhibitors may have a potential role in inhibiting sympathetic excitation. A case report of a patient with diabetes and heart failure also suggested that a 123I-MIBG scan after iglizin treatment showed significant improvement in SNS at 12 months of follow-up compared to baseline [10]. Wataru Shimizu et al. [11] demonstrated for the first time in a clinical trial that the administration of SGLT2i to diabetic patients with acute myocardial infarction (AMI) effectively improved SNS activity without causing any side effects. A recent study showed that, compared with placebo, the combination of SGLT2 inhibitors and angiotensin receptor blockers (ARBs) had a stronger blood pressure lowering effect than either drug alone, further suggesting that the two may have the same mechanism of action, namely reduced SNS activity and arterial stiffness[12].

5. Potential mechanism

5.1. Improve kidney function

The heart and kidneys are closely linked, and when a malfunction in one organ leads to a malfunction in the other, this is called cardio-renal syndrome [13]. Statistics have found that up to 60% of patients with heart failure have concurrent chronic kidney disease, and the risk of death is significantly increased compared to patients with heart failure alone [14]. In 2019, Vlado Perkovic et al. [15] first found that caglizin reduced patients' risk of death from renal causes by 34% and the risk of developing end-stage renal disease by 32%. Herat et al. [16] suggested that there was a bidirectional relationship between SGLT2 inhibitors and SNS activity, that SGLT2 inhibitors promoted the decrease of SNS activity in the heart and kidneys, and that the decreased SNS activity in turn weakened the renal expression of SGLT2. Cardio-renal syndrome severely limits drug options for patients with heart failure, such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor antagonists (ARBs), which can lead to acute kidney injury and the risk of hyperkalemia, and SGLT2i can directly address this problem [17].

5.2. Regulation of the central autonomic nervous system

SGLT2 is highly expressed in the brain, primarily in the microvessels of the blood-brain barrier, but also in the amygdala, hypothalamus, periaqueductal gray matter (PAG), and nucleus tractus solitarius (NTS), locations that have also been shown to be responsible for learning processes, food intake, energy metabolism, and central autonomic regulation [18]. SGLT2i is fat-soluble and can cross the blood-brain barrier to act directly on the target. Thiquynhnga Nguyen et al. found that c-Fos was widely expressed in the whole central autonomic nervous region by western blotting of brain tissue in mice fed SGLT-2i. It was also suggested that SGLT-2i may act on the ventrolateral region of the head of the medulla oblongata network (RVLM) and affect the outflow of preganglionic neurons to the medial lateral nucleus of the spinal cord (IML), thereby promoting parasympathetic activity[19].

5.3. Improve energy metabolism

The heart needs a lot of energy to maintain normal systolic function. Healthy cardiomyocytes can use a variety of substances to produce Energy, including glucose, fatty acids, ketone bodies, and amino acids. Oxidation of free fatty acids (FFA) can provide 70% to 90% of ATP, and ketone bodies only a small part [20]. However, when cardiomyocytes are damaged, energy metabolism changes, and ketone bodies other than glucose and fatty acids become the main energy-producing substances of cardiomyocytes. In a pig model of heart failure induced by left anterior descending branch occlusion, Englipzin reduced glucose utilization and increased ketone, fatty acid, and branched-chain amino acid utilization, thereby improving myocardial metabolism, enhancing left ventricular systolic

function, and alleviating myocardial remodeling[21]. Chang-Myung Oh et al., in a mouse model of adriamycin-induced heart failure, found that enaglitizn induced plasma β -hydroxybutyric acid and ATP production to provide adequate myocardial energy reserve, which is an important protective factor for heart failure [22]. However, Jonas Oldgren et al. investigated myocardial metabolism in diabetic patients without heart failure. Found limited Effects of 6 weeks of treatment with dapagliflozin on myocardial function, myocardial work efficiency and cardiac fatty acid uptake [23].

5.4. Reduce the inflammatory response

Inflammation is also one of the determining factors in the course of heart failure. Studies have confirmed[24], Dapagliflozin could significantly inhibit the increase of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and other pro-inflammatory cytokines. The effect of SGLT-2i on the inflammatory process may be related to the inhibition of inflammatory related molecular pathways. Koyani et al. [25] found that in isolated cardiomyocytes and macrophages, enagliflozin reduces inflammation by activating the adenylyate activated protein kinase pathway. So Ra Kim et al.[26] found that SGLT-2i blocked further secretion of pro-inflammatory factor IL-6 by macrophages by inhibiting NLRP3 inflammasome activation. Detmar Kolijn et al. found that in a mouse model of heart failure with ejection fraction retention, enaglitide reduced levels of ICAM-1, VCAM-1, TNF- α and IL-6, while improving vascular endothelial dilation function.

5.5. Inhibition of myocardial NHE

Na⁺ / H⁺ exchanger (NHE) is a protein distributed on the surface of cell membrane, which plays a role in regulating the pH value and the current of sodium and calcium in cardiomyocytes, and maintains the stability of the nervous conduction system and cardiovascular system. Yeves et al [27] have confirmed that the occurrence and development of heart failure is related to the sudden increase of NHE activity in the heart. Naglipzin can inhibit the activity of cardiac natrium-hydrogen exchanger, and then reduce the concentration of sodium and calcium ions in the cytoplasm of myocardium cells. Meanwhile, inhibiting the natriuretic agent and endogenous natriuretic peptide sensitivity can be improved[28]. However, it is unclear whether the benefit of SGLT-2i in heart failure comes directly from inhibition of cardiac NHE, evidence from clinical studies is lacking.

6. Conclusions

In summary, SGLT2i can effectively improve symptoms in patients with heart failure by affecting the function of autonomic nerves. However, there are few direct studies on the effects of SGLT2i on the cardiovascular autonomic nervous system, and there is still a lack of experimental evidence to confirm the specific mechanism of action between the two. At the same time, the relationship between SGLT2i and other autonomic drugs is still to be studied. The author believes that with more in-depth research, the application scope of SGLT2i will be further expanded, which will provide a more theoretical basis for clinicians to diagnose, treat, and prognostic analysis of cardiovascular diseases.

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