Naunyn-Schmiedeberg's Archives of Pharmacology (2024) 397:1037–1044
https://doi.org/10.1007/s00210-023-02655-7

RESEARCH

Empagliflozin improves cardiac function in rats with chronic heart failure

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Received: 25 June 2023 / Accepted: 30 July 2023 / Published online: 11 August 2023

Abstract

The objective of this study is to examine the effect of empagliflozin on cardiac function in rats with chronic heart failure and the possible mechanism. Forty 6-week-old male SD rats were randomly divided into the control group, empagliflozin treatment group, and sham-operated group. SD rats in the control group and empagliflozin treatment group were subjected to ligation of the anterior descending coronary artery to induce an acute myocardial infarction model. SD rats in the sham-operated group were only subjected to threading of the anterior descending branch of the coronary artery without ligation. On the second day after surgery, the control group and sham operation group were given physiological saline by gavage, while the empagliflozin treatment group was given empagliflozin (30 mg/kg/day) by gavage. Sixteen weeks later, cardiac function, intracellular reactive oxygen species (ROS) levels, mitochondrial membrane potential (MMP), serum brain natriuretic peptide, hypersensitive C-reactive protein (hs-CRP), iNOS expression levels, and myocardial morphological changes were observed. Compared with that in the control group, heart function in the empagliflozin-treated group was significantly improved, MMP was increased, intracellular ROS levels were decreased, and NT-proBNP and hs-CRP were significantly reduced, and HE staining showed that the cell oedema was less than that in the control group, tissue arrangement was more orderly, and iNOS expression was inhibited. Empagliflozin can improve cardiac function in rats with chronic heart failure, and the mechanism may involve inhibiting inflammation, reducing myocardial oxidative stress, and improving myocardial fibrosis.

Keywords Chronic heart failure · Empagliflozin · Reactive oxygen species · Hypersensitive C-reactive protein · Membrane potential

With the ageing of the population in China and the increasing incidence of cardiovascular diseases (CVDs) such as coronary heart disease, atrial fibrillation, and hypertension, the number of patients with heart failure (HF) is increasing yearly. Chronic heart failure (CHF) is the final stage of various heart diseases and the final stage for CVD prevention and control. It is estimated that the current number of CVD patients is 290 million (Hu et al. 2019). At present, there are over 13.7 million HF patients (with a prevalence rate of 1.3%) in China (Hao et al. 2019), resulting in a huge burden on the social and economic health of the country. HF has a high incidence rate and mortality. The 1-year mortality of CHF patients is 7.2%, and the 1-year hospitalization rate is 31.9%, while the mortality and hospitalization rates of acute HF patients are as high as 17.4% and 43.9%, respectively (Murphy et al. 2020). Although significant breakthroughs have been made in the treatment of HF in the past decade, the incidence rate and mortality of HF patients are still high (Simpson et al. 2020; Uchmanowicz et al. 2020). Currently, the treatment of HF remains a major challenge in cardiology.

Diabetes is an independent risk factor for HF. Every 1% increase in glycosylated haemoglobin can increase the incidence rate of HF from 8 to 36%. In recent years, the novel hypoglycaemic drug sodium glucose cotransporter 2 inhibitor (SGLT-2i) has shown significant cardiovascular benefits, and SGLT-2i has been included in the 2021 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. The pathogenesis of HF is relatively complex. At present, treatment of HF

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has shifted from traditional cardiac strengthening, diuresis, and vasodilation by targeting the body's haemodynamics to treatment based on neurofumoral mechanisms. Treatment options mainly include renin angiotensin aldosterone system (RAAS) inhibitors, β receptor blockers, aldosterone receptor antagonists, positive inotropic drugs, and diuretics (Packer et al. 2020); previous studies have shown that dapagliflozin reduces blood volume, increases haematocrit, and enhances the oxygen carrying capacity of the body (Testani et al. 2010; Kataoka 2019; Ohara et al. 2019). The DAPA-HF test and the latest EMPEROR Reduced test showed that SGLT-2 inhibitors could reduce the risk of cardiovascular death or the composite event endpoint of hospitalization due to HF in patients with HF with reduced ejection fraction (EF%), whether these patients had diabetes or not (Zannad et al. 2020). In addition, CANTOS research has shown that inflammation is an important cardiovascular risk factor, and anti-inflammatory treatment can improve the prognosis of CVDs (Ridker et al. 2017). However, the mechanism by which empagliflozin can treat CHF is not clear. Thus, we established a CHF rat model by ligating the anterior descending branch of the coronary artery in SD rats to study the effect of empagliflozin on heart function during CHF and the possible mechanisms.

Materials and methods

Groupings and processing

The animal experiment was carried out in strict accordance with the "Regulations on the Management of Experimental Animals" issued by the State Council of the People's Republic of China. This experiment was approved by the Experimental Animal Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. Male SD rats were provided by Chongqing Medical University and were randomly divided into a control group of 15 rats (AMI + NS), an empagliflozin-treated group of 14 rats (AMI + empagliflozin), and a sham-operated group of 11 rats (sham-operated + NS). The ischaemic HF model was established as previously described (Wu et al. 2014) by ligating the left anterior descending artery in the control group and the empagliflozin-treated group. The sham-operated group was only subjected to threading without ligation at the same site. Postoperative intraperitoneal injection of penicillin (4000 U/day * 3 days) was performed to prevent infection. On the second day after surgery, the control group and sham operation group were given physiological saline by gavage, while the treatment group was given empagliflozin (30 mg/kg/day) by gavage for a total of 16 weeks.

Empagliflozin (10 mg/tablet) was purchased from Shanghai Bollinger Ingerhan Pharmaceutical Co., Ltd. The rat hypersensitive C-reactive protein (hs-CRP) enzyme-linked immunosorbent assay (ELISA) kit was purchased from Shenzhen Zike Biotechnology Co., Ltd. The IP lysis buffer was obtained from Shanghai Biyuntian Biotechnology Co., Ltd., and the N-terminal pro-B-type natriuretic peptide (NT-proBNP) ELISA kit for rats was purchased from Shanghai Xitang Biotechnology Co., Ltd. iNOS antibodies (Beijing Boorsen Biotechnology Co., Ltd.), the HX-200 animal ventilator (Chengdu Taimeng Technology Co., Ltd.), and the Vivid Doppler ultrasound instrument (probe frequency 10 MHz, GE company) were used.

Echocardiographic detection of cardiac function and specimen collection

After 16 weeks of gavage, SD rats were intraperitoneally anaesthetized with chloral hydrate, placed on their backs, and fixed on the operating table. The cardiac function of each group of rats was measured by ultrasound. The long axis of the left ventricle was displayed on a two-dimensional ultrasound section, and M-ultrasound was used to measure the left ventricular end diastolic diameter (LVIDd), left ventricular internal diameter (LVIDs), and EF%. After the cardiac function testing, blood was collected from the inferior vena cava, the rats were decapitated, and the heart was removed by thoracotomy. The tissues were washed with physiological saline, and vascular tissue, the atrium, the right ventricle, and fibrotic areas were removed after left ventricular infarction. The remaining noninfarcted myocardium of the left ventricle was prepared into paraffin sections, and the remaining portion was stored in liquid nitrogen for later use. Blood was collected at 950 days, centrifuged for 20 min to extract the supernatant, and stored at − 20 ℃ for future use.

Intracellular reactive oxygen species (ROS) levels and mitochondrial membrane potential (MMP) were measured by flow cytometry

Twenty milligrams of noninfarcted left ventricular myocardial tissue was cut into 1–2 mm fragments with ophthalmic scissors, 2 ml of 0.25% trypsin was added, and the tissue was digested in a 37 °C water bath for 3 min, centrifuged at 500 r for 1 min. Then, 1 ml of foetal bovine serum was added to terminate the digestion. The differential adhesion method was used to separate myocardial cells, and a cell counting plate was used to count the number of myocardial cells. Each group contained 1.0×10^6 resuspended cells suspended in DCFH-DA diluted 1:1000 with serum-free culture medium. A total of 1.0×10^6 resuspended cells were added to 0.5 ml of Rh123 staining solution, and ROS levels and the MMP were detected by flow cytometry.

ELISA analysis of blood BNP levels

The preserved SD rat plasma was tested according to the instructions of the rat BNP kit.

ELISA analysis of blood hs-CRP levels

The preserved SD rat plasma was diluted appropriately and analyzed according to the kit instructions. The absorbance value was measured using ELISA at a wavelength of 450 nm, and a standard curve was drawn using the standard sample provided by the kit. Serum levels of hs-CRP in each group were calculated, and each sample was examined 3 times.

HE staining and immunohistochemical analysis of iNOS expression

Rat myocardial tissue was fixed with 4% paraformaldehyde for 24 h and embedded in paraffin (5 μm) for HE staining. The immunohistochemical steps were carried out according to the kit instructions (Beijing Zhongshan Jinqiao Company). The paraffin sections were dewaxed with xylene and rehydrated through a gradient, and antigen repair was performed with citric acid solution. Goat serum sealing was performed at room temperature for 1 h, and diluted rabbit-derived iNOS polyclonal antibodies (1:250) were added dropwise. The samples were incubated overnight at 4 °C. Goat anti-rabbit secondary antibodies were added the next day. The horseradish enzyme-labelled albumin working solution (S-A/HRP) was incubated at room temperature for 30 min, followed by DAB staining and haematoxylin staining. The film was sealed, and myocardial morphology and iNOS expression were observed under a microscope. The integrated optical density (IOD) of iNOS-positive myocardial cells in each group was measured using Image-Pro Plus (IPP) software to determine the relative protein expression of iNOS.

Statistical analysis

The experimental data were analyzed with SPSS 21.0 statistical software, and the experimental results were subjected to a normal distribution. Indicators with a normal distribution and homogeneity of variance between groups were compared by ANOVA; otherwise, the rank sum test was used. The difference was statistically significant at $P < 0.05$.

Results

Feeding situation

Eight SD rats in the model group died, and one rat in the sham surgery group died. The causes of death were infection, acute left HF, and malignant arrhythmia. The remaining 31 SD rats reached the experimental endpoint.

Cardiac function test results

At 16 weeks after ligation of the left anterior descending artery, the control group showed a significant increase in LVIDd and LVIDs ($P < 0.05$) compared with the sham-operated group, while LVEF decreased significantly ($P < 0.05$). Compared with the control group, the empagliflozin treatment group showed a significant reduction in LVIDd and LVIDs ($P < 0.05$) and a significant increase in LVEF ($P < 0.05$), as shown in Table 1 and Fig. 1.

Myocardial ROS and MMP

Compared with the sham surgery group (107.14 ± 4.79), the control group (196.85 ± 12.25) and empagliflozin-treated group (133.16 ± 12.25) showed significant increases in intracellular ROS in myocardial cells ($P < 0.05$). The empagliflozin treatment group showed a significant decrease compared to the control group ($P < 0.05$). Compared with that in the sham operation

Table 1 Echocardiographic parameters of rats with HF following MI ($\chi \pm s$)

	Sham group	Control group	Empagliflozin group
4 weeks following MI			
LVIDd (cm)	0.55 ± 0.04	0.69 ± 0.11^{a}	0.64 ± 0.04^{b}
LVIDs (cm)	0.26 ± 0.09	0.55 ± 0.11^{a}	0.47 ± 0.11^{b}
LVEF (%)	90.9 ± 2.74	73.3 ± 8.21^{a}	76.9 ± 3.79^{b}
16 weeks following MI			
LVIDd (cm)	0.52 ± 0.03	0.73 ± 0.09^{a}	0.57 ± 0.04^{b}
LVIDs (cm)	0.21 ± 0.04	0.5 ± 0.11^{a}	0.28 ± 0.06^{b}
LVEF (%)	92.5 ± 3.03	70.5 ± 9.54^{a}	85.1 ± 6.37^{b}

[a]$P < 0.05$, compared with the sham group; [b]$P < 0.05$, compared with the control group

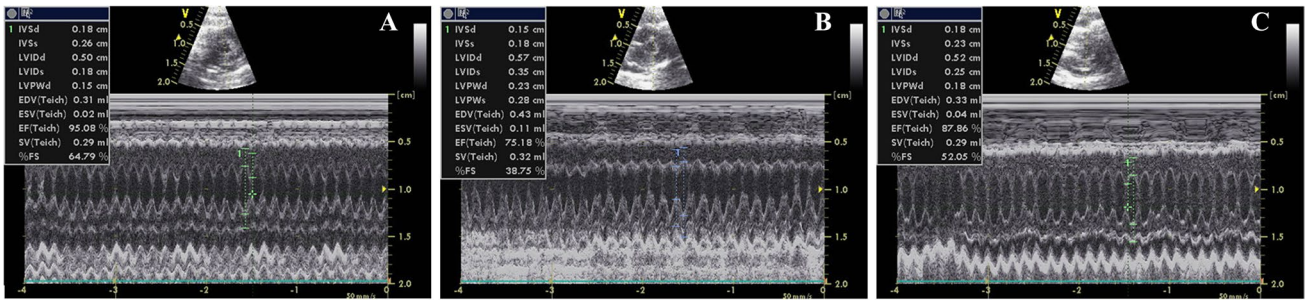

Fig. 1 Echocardiographic measurements of the rats in the different groups (16 weeks). **A** Normal cardiac function in the sham group. **B** Diminished cardiac function in the AMI group. **C** Improved cardiac function in the empagliflozin group compared with the AMI group

group (104.73 ± 4.31), the MMP in the control group (32.76 ± 7.7) and empagliflozin treatment group (80.21 ± 14.98) decreased. The empagliflozin treatment group showed an increase compared to the control group, as shown in Fig. 2.

Serum BNP levels

Compared to those in the sham surgery group (8.76 ± 0.46 μg/L), serum BNP levels were significantly increased in the control group (22.7 ± 1.23 μg/L) and empagliflozin treatment group (13.5 ± 0.59 μg/L) ($P < 0.05$). The empagliflozin treatment group showed a significant decrease compared to the control group ($P < 0.05$).

Serum levels of hs-CRP

Compared to those in the sham surgery group (10.1 ± 0.37 μg/L), serum BNP levels were significantly increased in the control group (29.4 ± 1.02 μg/L) and empagliflozin treatment group (14.3 ± 0.53 μg/L) ($P < 0.05$). The empagliflozin treatment group showed a significant decrease compared to the control group ($P < 0.05$).

HE staining and iNOS expression in the myocardium of rats in each group

HE staining showed that in the sham surgery group [percentage of oedematous cells among total cells: (12 ± 0.13)%], the myocardial fibres were arranged neatly, the cytoplasm was rich and uniform, and the nucleus was intact. The control

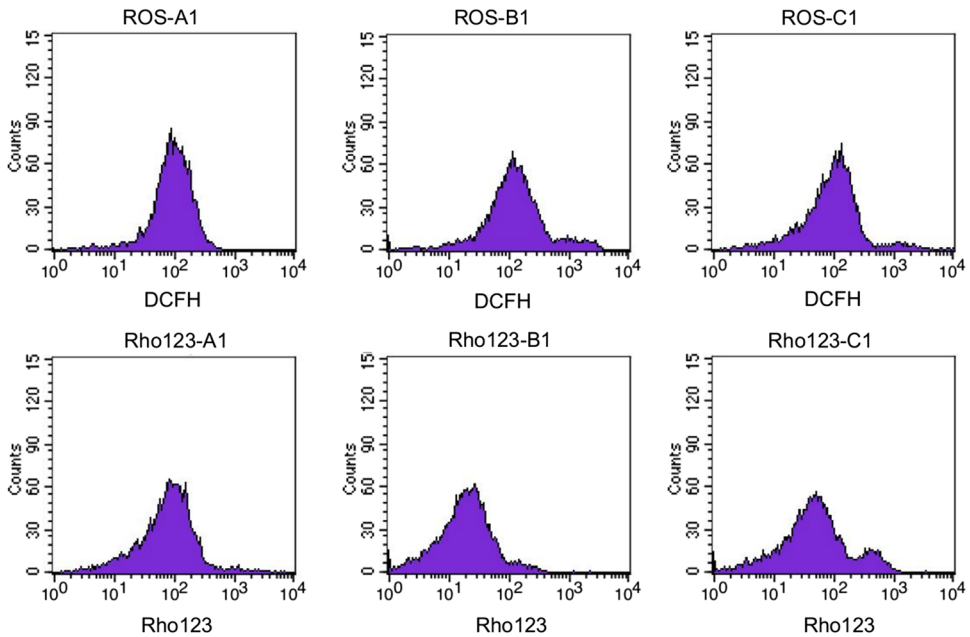

Fig. 2 ROS levels and MMP level in the myocardial cells of rats in each group. A1. Sham surgery group. B1. Control group. C1. Empagliflozin treatment group

group showed significant myocardial tissue oedema compared to the sham surgery group [percentage: (79 ± 0.53)%] ($P < 0.05$), and the myocardial fibres were broken and disordered, there was nuclear disappearance, and a large amount of fibrous tissue formed around the infarcted area. Compared with that in the control group, myocardial tissue oedema in the empagliflozin treatment group was significantly reduced [percentage: (31 ± 0.29)%] ($P < 0.05$). The arrangement was relatively neat, the nucleus was relatively intact, and fibrosis around the infarction was reduced, as shown in Fig. 3.

The expression level of iNOS [IOD (15.67 ± 2.41)] in the sham operation group was very low, while the expression level of iNOS in the control group [IOD (1254 ± 23.18)] and empagliflozin treatment group [IOD 109.83 ± 15.09)] was significantly higher than that in the sham operation group ($P < 0.05$); the expression level of iNOS in the empagliflozin treatment group was significantly lower than that in the control group ($P < 0.05$), as shown in Fig. 3.

Discussion

In this study, it was found that empagliflozin had anti-inflammatory effects, reduced myocardial oxidative stress, stabilized cell membrane potential, and inhibited myocardial fibrosis, thereby improving heart function in rats with HF.

Empagliflozin is a novel oral hypoglycaemic drug that is an SGLT2i. SGLT2i drugs mainly inhibit the reabsorption of sodium and glucose by SGLT2 in the renal tubules. They can promote the excretion of sodium in urine while excreting sugar and have an osmotic diuretic effect, thus causing a mild antihypertensive effect (Kalluri et al. 2021). In the reanalysis of the subjects in the EMPEROR Reduced study, the researchers found that when blood pressure was less than 110 mmHg, treatment with empagliflozin did not reduce blood pressure but rather slightly increased blood pressure (Böhm et al. 2021). In this experimental study, I observed that empagliflozin has a mild antihypertensive effect on heart failure rats. However, even if the baseline blood pressure level of heart failure rats is low, empagliflozin treatment is still safe and effective.

According to the previous EMPEROR series of studies, regardless of the eGFR of patients (as low as 20 mL/min/1.73 m^2), empagliflozin can reduce cardiovascular events and delay the progression of renal function deterioration, which has shown clear benefits in heart failure and CKD (Böhm et al. 2022).The EMPEROR series studies analyzed the relationship between heart rate (HR) and the outcome of heart failure in patients with LVEF > 40%, as well as the impact of empagliflozin on patients. It is well known that an increased HR means increased sympathetic nervous system excitability and catecholamine levels. There is currently evidence that resting HR is an important predictive factor for cardiovascular complications and mortality, especially in patients with chronic heart failure. The EMPEROR Preserved analysis showed that HR could predict the outcome of heart failure in HFpEF and HFmrEF patients with sinus rhythm (non-atrial fibrillation). While

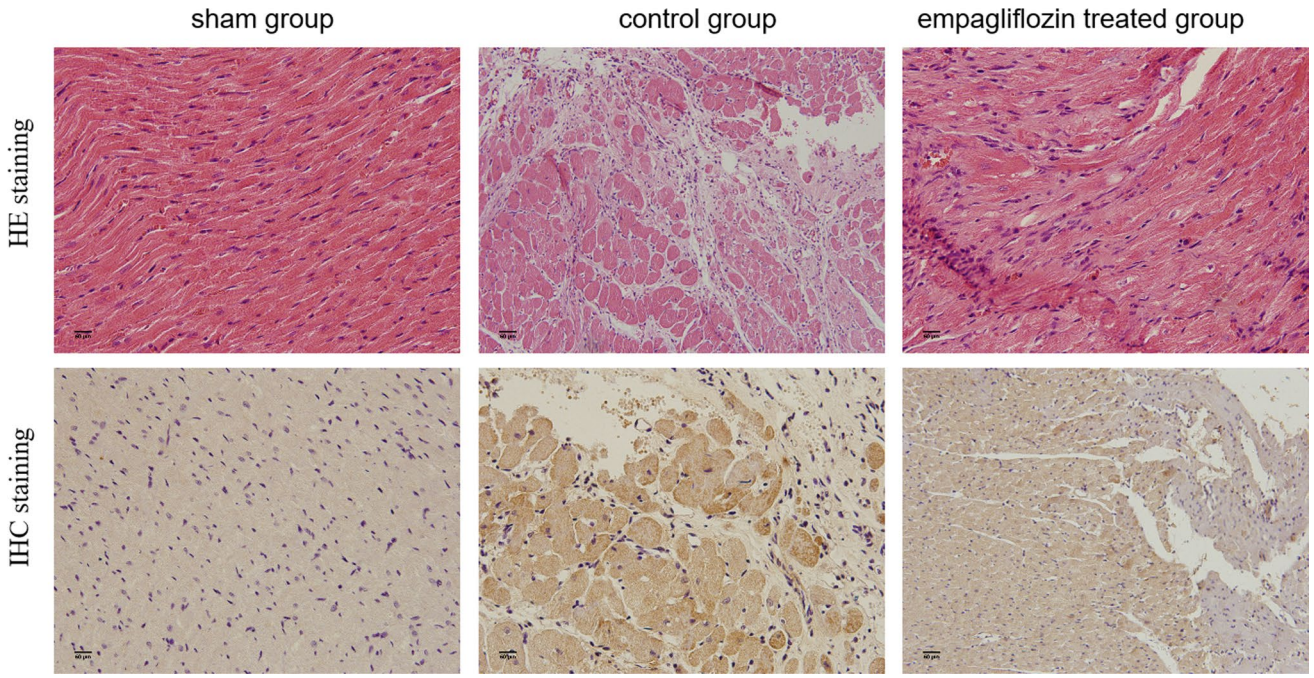

Fig. 3 Myocardial samples of the area surrounding of the infarction, as visualized by HE staining (HE × 400) and IHC staining (× 400)

empagliflozin reduced the main outcomes (cardiovascular death and the first incidence of HF), the time of the first occurrence of HF, and the treatment effect of recurrent HF in HFpEF and HFmrEF patients, the treatment had no effect on HR, which indicates that empagliflozin does not activate the sympathetic nervous system while improving the prognosis of heart failure, resulting in a faster HR (Habal et al. 2014).

It has been reported that the blood ketone body concentration is significantly elevated regardless of the presence or absence of diabetes. The mechanism by which SGLT2 inhibitors increase blood ketone body concentrations is related to the following factors: (1) SGLT2 inhibitors cause an increase in glucagon/insulin, leading to the accumulation of ketone bodies in the body. SGLT2 inhibitors directly or indirectly regulate glucagon expression, resulting in the accumulation of ketone bodies. (2) SGLT2 inhibitors promote fatty acid oxidation to produce ketones. (3) SGLT2 inhibitors inhibit renal clearance of ketone bodies. The clearance rate of ketones decreases, and ketones accumulate. (4) The osmotic diuretic effect of SGLT2 inhibitors leads to hypovolemia, and dehydration leads to increased concentrations of lipolytic hormone and increases in the production of ketone bodies (Ferrannini et al. 2014; Bonner et al. 2015; Perry et al. 2019; Yokono et al. 2014; Mende 2022). However, Tang et al. included 10 RCTs involving 13,134 patients and 14 DKA events. Compared with the control group, the risk of DKA did not significantly increase in the SGLT2i group (OR = 1.71, 95% CI 0.56–5.20) (Tang et al. 2016). Therefore, SGLT2i drugs have good safety.

Previous studies have shown that SGLT-2i can significantly reduce the risk of cardiovascular death and hospitalization rate for HF, but the mechanism of action is still not fully understood. Research has shown that oxidative stress is present in almost all forms of CVD and plays a crucial role in energy regulation within myocardial cells. Oxidative stress is defined as a state in which cells and/or the body produce excessive ROS that exceed endogenous antioxidant defence capabilities, thereby damaging proteins, lipids, and DNA. Active oxygen includes superoxide (O-2 ·), hypochlorite (HOCl), and hydrogen peroxide (H2O2). Under normal physiological conditions, the generation of ROS in the heart is minimal, and there is an antioxidant defence system that clears ROS to maintain metabolic balance. However, in response to certain harmful stimuli, cardiac oxidative antioxidant homeostasis is disrupted, and the accumulated O-2 · is highly diffused and damages myocardial cells (Halliwell 2006; Palmieri et al. 2015). In addition, ROS can reduce myocardial cell contraction in a concentration-dependent manner (Kwon et al. 2003; Sabri et al. 1998), leading to a certain degree of cardiac dysfunction (Wu et al. 2019; Canton et al. 2004). This study showed a significant increase in myocardial ROS levels in rats with CHF, confirming that CHF rats were in a state of oxidative stress at this time, while myocardial ROS levels in rats treated with empagliflozin were significantly lower than those in the control group. Oxidative stress plays an important role in the occurrence and development of HF; it can mediate cell proliferation, myocardial remodelling, and myocardial apoptosis by activating various signalling pathways, thereby causing further deterioration of cardiac function. Moreover, the role of mitochondrial dysfunction in CVDs has been fully confirmed. A decrease in the MMP is a sign of early apoptosis. This study showed that the MMP of CHF rats was lower than that of sham rats, the MMP of CHF rats was higher than that of control rats after treatment with empagliflozin, and intracellular ROS levels were lower than those in the control group. These results suggested that empagliflozin could stabilize MMP, improve mitochondrial function, and increase left ventricular EF% in rats with HF by reducing myocardial ROS production. Empagliflozin can reduce myocardial cell apoptosis and improve cardiac function in HF rats. These results are consistent with previous studies showing that empagliflozin reduces oxidative stress and improves cardiac function (Lee et al. 2017; Tanajak et al. 2018).

Inflammation is an important factor in the severity of CHF. The increase in proinflammatory biomarkers in patients with HF is related to disease severity. Inflammatory cytokines not only lead to endothelial dysfunction but also increase the development of myocardial fibrosis (Briasoulis et al. 2016). Previous studies have shown that inflammation plays a crucial role in ischaemic myocardial damage, leading to the deterioration of cardiac structure and function, thereby promoting structural changes and functional decline in ischaemic heart disease (Wilhelmi et al. 2005). Inflammatory reactions are present during the entire occurrence and development of HF in patients. hs-CRP, which is a biomarker of inflammation, was significantly elevated in the serum of CHF rats compared to sham-operated rats. The serum levels of hs-CRP in the empagliflozin-treated group were decreased compared to those in the control group, indicating that empagliflozin has anti-inflammatory effects. Furthermore, this study showed that myocardial fibres in HF rats were disrupted and arranged in a disordered manner, which was accompanied by the disappearance of cell nuclei and the formation of a large amount of fibrous tissue around the infarcted area. After treatment with empagliflozin, myocardial cell tissue oedema in HF rats was significantly reduced, and fibrosis around the infarcted area was reduced, indicating that empagliflozin could inhibit myocardial fibrosis. In addition, studies have shown a significant increase in iNOS levels in the myocardial cells of patients with HF (Umar and Laarse 2010; Li and Olshansky 2011). INOS can catalyze the synthesis of excess NO from L-arginine, which in turn reacts with O2 to form the strong oxidant peroxynitrite ion (ONOO-), which can cause tissue damage and

participate in the development of CHF (Giordano 2005). The results of this study showed a significant increase in iNOS levels in the myocardial tissue of HF rats compared to sham-operated rats, which is consistent with the significant increase in iNOS levels in the myocardium of HF patients reported by Umar (Umar and Laarse 2010). However, iNOS levels in the myocardial tissue of HF rats were significantly decreased after treatment with empagliflozin. This finding suggests that empagliflozin can alleviate oxidative stress in CHF rats by downregulating iNOS expression, thereby improving cardiac function in CHF rats.

In summary, empagliflozin ameliorated cardiovascular risk factors and played a role in cardiovascular protection by exerting anti-inflammatory effects, reducing oxidative stress, stabilizing cell membrane potential, inhibiting myocardial fibrosis, and increasing the EF% and other mechanisms. However, its mechanism of action is still not fully understood. We believe that with further research, the mechanism by which empagliflozin affects CHF will be revealed, providing new therapeutic targets for CHF.

Conclusion

This study demonstrated that empagliflozin improves cardiac function in the context of CHF. Its mechanism may be related to inhibiting inflammation, reducing myocardial oxidative stress, and improving myocardial fibrosis.

Authors contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Zhenzhen Wang, QianLiu, Xiaofang Wang, Pengpeng Wang, Fenglei Zhang, and Zhuwen Wang. The first draft of the manuscript was written by Zhenzhen Wang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

Funding This work was supported by Shandong Province Medical and Health Technology Development Plan Project.

Data availability All source data for this study are available upon reasonable request from the authors.

Declarations

Ethical approval The animal experiment was carried out in strict accordance with the "Regulations on the Management of Experimental Animals" issued by the State Council of the People's Republic of China. This experiment was approved by the Experimental Animal Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University.

Informed consent Not applicable.

Competing interests The authors declare no competing interests.

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