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Cardiac effects of empagliflozin in heart failure with preserved ejection fraction

Kolijn D, Pabel S, Tian Y, Lódi M, Herwig M, Carrizzo A, et al. Empagliflozin improves endothelial and cardiomyocyte function in human heart failure with preserved ejection fraction via reduced pro-inflammatory-oxidative pathways and protein kinase Gα oxidation. Cardiovasc Res 2020;cvaa123**. doi: 10.1093/cvr/cvaa123.**

Empagliflozin belongs to a groups of antidiabetic drugs which inhibit the type 2 sodium-glucose cotransporter (SGLT2). Previous clinical studies demonstrated that use of SGLT2 inhibitors in diabetic patients at high cardiovascular risk reduces the risk of cardiovascular events, and improves heart failure. It also reduces the risk of cardiovascular death in heart failure patients independently of diabetes. Different mechanisms have been suggested to explain its effect, such as weight and blood pressure reduction, decreased blood sugar levels, increased renal excretion of water and sodium and improved vascular function. However, different works demonstrate that the cardiac effects of SGLT2 inhibitors are independent of cardiovascular risk factors. Moreover, both diabetes and other risk factors are common causes of heart failure with preserved ejection fraction (HFpEF), affecting a large group of patients without effective pharmacological treatment. It is therefore necessary to know the possible direct cardiac mechanisms of "gliflozins" to understand which patients could benefit from their use.

In this work, Kolijn et al. studied the mechanisms involved in the acute cardiovascular benefits of empagliflozin in the cardiac tissue of patients with HFpEF and obese ZDF rats. Using Western blot and ELISA techniques they observed that both in human and rat myocardium, empagliflozin has an anti-inflammatory effect, reducing ICAM-1, VCAM-1, TNF-α and IL-6 levels. In addition, it attenuates oxidative stress parameters, such as H2O2, 3-nitrotyrosine, GSH and lipid peroxide, which are increased in HFpEF. Another significant contribution of this work is that empagliflozin prevents eNOS function uncoupling, reducing PKG1α oxidation and polymerization and allowing its translocation from the sarcolemma back to the cytosol. As a result of nitric oxide level and GC and PKG1α function restoration, there is higher phosphorylation of myofilament proteins, such as titin and troponin I. As a whole, these molecular effects were reflected in an improved endothelial vasorelaxation and reduction of myocyte stiffness in both patient and rat samples. Linear regression analyses demonstrated an association between oxidative stress and PKG1α polymerization with cardiomyocyte stiffness and diastolic dysfunction of patients with HFpEF, suggesting that this is the main mechanism through which empagliflozin improves cardiac function in this group of patients.

There are currently very limited treatment options for patients with HFpEF, with no drug having shown to be effective to treat diastolic dysfunction and improve patient prognosis. Therefore, management of this group of patients is limited to symptomatic and comorbidity therapy. Kolijn et al. provide solid evidence about the benefit of empagliflozin in improving the NO-SGC-cGMP signaling cascade and consequently reducing PKG1α oxidation. In addition, they show that the anti-inflammatory and antioxidant action of the drug is manifested by enhanced cardiomyocyte function in patients with HFpEF, independently of blood sugar levels. Thus, this study provides basic information on very interesting molecular mechanisms that support previous clinical findings and will promote future studies of this group of drugs as a potential treatment of heart failure.

Ethical considerations

Not applicable.