P4466

Empagliflozin improves heart function after myocardial infarction in the rat

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Background: Selective Sodium-glucose cotransporter 2 (SGLT2) inhibition with Empagliflozin reduced progression of left ventricular dysfunction and improved tolerance of physical exercise in heart failure by normoglycemic rats. Here, we hypothesized that Empagliflozin prevents cardiac dysfunction after myocardial infarction (MI).

Purpose: This study aimed to investigate whether Empagliflozin protects the heart in the early phase after experimental MI in normoglycemic rats.

Methods: MI was induced in Wistar rats via permanent ligation of the left coronary artery. Treatment with Empagliflozin (1 mg/kg/daily per os) was started after MI and continued for 7 days. Sham operated and vehicle treated animals served as controls (n=8). Hemodynamic parameters were measured via transthoracic echocardiography and intracardiac Samba catheter. Glucose concentration was determined in serum and urine. Protein expression of Na+/H+ exchanger isoform-1 (NHE-1), sodium bicarbonate co-transporter (NBC), Sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA), transforming growth factor beta 1 (TGF-beta1), Smad2 in the left ventricle were also studied. Additionally, NHE-1 regulation was investigated in cardiomyocyte cell line H9c2.

Results: Systolic heart function was improved in Empagliflozin treated MI animals compared to vehicle as demonstrated by Global Longitudinal Strain (GLS) (20,9% vs. 16,6%; $p<0.05$). E/A ratio was decreased by tendency and blood pressure was not affected. Ejection fraction ($p<0.05$), fractional shortening ($p<0.05$), stroke volume ($p<0.01$) were increased in Empagliflozin treated control rats as compared with the sham group. Moreover, application of Empagliflozin (1mg/kg, i.v. bolus) to healthy rats in 30 min increased maximal pressure in the left ventricle as compared with vehicle (110,5±15,3 mmHg vs 79,1±11,9 mmHg; $p<0.05$). Parallel, dP/dtmax was increased while dP/dtmin was decreased by tendency. Empagliflozin treatment did not affect glucose concentration in serum and urine. Treatment of cardiac H9c2 cells with Empagliflozin (1μM) down-regulated NHE-1 by 27%.

Conclusion: SGLT2 inhibitor Empagliflozin improved systolic function in the early phase post MI independently from glucose regulation. The cardioprotective mechanisms of SGLT2 inhibitors may involve cardiac NHE-1 exchanger inhibition.