

中文題目：Dapagliflozin 改善二尖瓣逆流心衰竭之血型動力學以及心律不整機制探討

英文題目：Dapagliflozin improves cardiac hemodynamics and mitigates arrhythmogenesis in mitral regurgitation-induced myocardial dysfunction

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Background: Mitral regurgitation (MR) is one major factor contributing to heart failure (HF). Despite the advancement of MR surgeries, it remains lacking an effective medical therapy to mitigate MR progression. Sodium glucose co-transporter 2 (SGLT2) inhibitor, a new class of anti-diabetic drugs, shows benefits in reduction of HF hospitalization and cardiovascular mortality but the mechanism remains unclear. We hypothesized that Dapagliflozin, a SGLT2 inhibitor, can improve cardiac hemodynamics in MR induced HF.

Methods and results: Using a novel and mini-invasive technique, we established a MR model in rats. MR induced left heart dilatation and functional decline exacerbated three weeks post induction. Half rats were randomized to be administered with Dapagliflozin at 10 mg/kg/day for 6 weeks. After evaluations of electrocardiography and echocardiography, invasive hemodynamic study was performed and followed by tissue analyses. Dapagliflozin restored the MR induced impairment of left ventricular ejection fraction, maximal velocity of pressure and the slope of end-systolic pressure volume relationship. Despite no significant changes of electrography at rest, rats treated with Dapagliflozin exhibited a lower inducibility and maintenance of pacing-induced atrial fibrillation. In histological analysis, Dapagliflozin significantly attenuated cardiac fibrosis and cardiac expressions of apoptosis associated proteins including Bax, cleaved caspase 3 and increased Bcl-2. Mechanistically, we also showed that dapagliflozin significantly reduced ER stress-associated proteins including GRP78, PERK, eIF-2 α , ATF-4, and CHOP.

Conclusions: Through suppressing cardiac fibrosis and ER stress associated proteins, Dapagliflozin improves hemodynamics in our MR induced HF rat model. Our results suggest the therapeutic potentials of Dapagliflozin in MR induced HF.

Keywords: SGLT2 inhibitor, Dapagliflozin, Mitral regurgitation, Heart failure, Cardiac fibrosis, ER stress, apoptosis