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THE COMBINATION OF PITAVASTAIN AND ISCHEMIC POSTCONDITIONING ATTENUATES MYOCARDIAL ISCHEMIC/REPERFUSION INJURY IN IMPAIRED GLUCOSE TOLERANCE RAT IN VIVO

Zhu Xueli, Wu Liming, Chen Lianglong *Department Of Cardiology, Union Hospital, Fujian Medical University, Fujian, China*

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Background and Objectives Myocardial ischemia-reperfusion injury (MIRI) can be alleviated by ischemia post-conditioning (IPC) and/or statin post-conditioning (SPC), and their combination. However, it is unclear how the cardio-protection works in impaired glucose tolerance (IGT) state since IGT significantly abolishes intrinsic myocardial self-protection, and

if it does so, what mechanisms are involved in the process. This study aims to investigate the cardio-protective effects and possible mechanisms by combination of SPC and IPC in the IGT rats.

Methods An IGT model was successfully created in 72 out of 117 male Wistar rats by injecting STZ, which were randomly allocated into six groups (n=12 per group): Sham group, treated with open chest operation but without myocardial ischemia as controls; I/R group, with ischemia 30 min and reperfusion 2 h in LAD territory but without other interventions; IPC group, treated with initial ischemia 30 min, then 3 consecutive runs of 10 s reperfusion/10s ischemia, and final reperfusion 2 h; SPC group, with initial ischemia 30 min, then pitavastatin (0.1 mg/kg) intravenously 3 min before reperfusion, and final reperfusion 2 h; ISPC group, with initial ischemia 30 min, then combination of three consecutive runs of 10 s reperfusion/10 s ischemia and pitavastatin 3 min before reperfusion, and final reperfusion 2 h; ISPC+LY294002 group, with initial ischemia 30 min, then combination of 3 consecutive runs of 10 s reperfusion/10 s ischemia, pitavastatin and PI3-K inhibitor LY294002 (0.3 mg/kg, intravenously) 3 and 15 mins before reperfusion, respectively.

Results Compared with sham group, I/R group had larger infarct size (70.1±3.1% vs 0±0%, p<0.05), and higher mitochondria score (3.24±0.74 vs 0.00±0.00, p<0.05). Compared with I/R group, IPC group, SPC group, and ISPC group all reduced myocardial infarct size (p<0.05, each) and CK-MB level (p<0.05, each), alleviated mitochondria injuries (p<0.05, each), and enhanced PI3K activation by up-regulated expression of phosphorylate Akt (p<0.05, each) and phosphorylate eNOS (p<0.05, each). Compared with IPC and SPC groups, ISPC group further reduced myocardial infarct size (33.4±6.5% vs 45.3±4.6%, p<0.05; vs 43.2±4.1%, p<0.05), CK-MB level (p<0.05, each) and mitochondria score (1.23±0.68 vs 2.28±0.77, p<0.05; vs 2.33±0.79, p<0.05) with more activation of PI3K evidenced by higher expression of phosphorylate Akt (p<0.05, each) and eNOS (p<0.05, each). However, compared with IPC, SPC and ISPC groups, phosphorylated Akt expression and phosphorylation levels of eNOS was significantly lower or undetectable in ISPC+LY294002 group (p<0.05, each), indicating that PI3K inhibiter LY294002 could completely block the PI3K-Akt-eNOS signaling pathway, resulting in abolishment of cardio-protection induced by IPC, SPC and their combination.

Conclusions The combination of pitavastain and ischemic postconditioning enhances the cardioprotection against myocardial ischaemia-reperfusion injury in impaired glucose tolerance rats, and PI3K-Akt-eNOS may be a major signaling pathway mediated this cardioprotection.