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 (1.28±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 inhibitor 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.
The combination of Pitavastain and ischemic postconditioning attenuates myocardial ischemic/reperfusion injury in impaired glucose tolerance rat in vivo

Zhu Xueli, Wu Liming and Chen Lianglong

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