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ISCHAEMIC POSTCONDITIONING PROTECTS CARDIOMYOCYTE FROM ISCHAEMIA/REPERFUSION INJURY BY ATTENUATING ENDOPLASMIC RETICULUM STRESS VIA PI3K-AKT PATHWAY

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PI3K-Akt Acute myocardial infarction (AMI) is one of the leading causes of death, demands early and complete reperfusion in therapy strategy. Reperfusion induces additional injury in the area at risk. Ischaemic postconditioning (IPO)are known as endogenous protective mechanism via activate the signaling of PI3K-Akt, could markedly limit myocardial infarction and resistant to the I/R injury. Recently study show that I/R can affect ER function-ER stress (ERs). ERs induces such as glucose-regulated proteins (GRPs), calreticulin (CRT) and so on, to protective for cell adaptation, when persistent or too intense, ERs will induce and activate ER proapoptosis fators such as CHOP, caspase-12, This study aimed to elucidate IPO whether attenuates I/R injury by suppressing ERs-induced apoptosisand if the phosphatidylinositol-3 kinase/Akt (PI3K/Akt) pathway is involved.

Methods 30 healthy adult male Wistar rats were assigned randomly into I/R group (A, I/R), ischaemia postconditioning group (B, IPO) and IPO+Wortmannin (C, IPO+Wortmannin), each group has 10 rats. Rats were used for Langendorff isolated heart perfusion. The hearts were subjected to global ischaemia for 30 min followed by 60 min reperfusion. Hearts treated by IPO were subjected to 10s episodes of 6 alternate myocardial ischaemia/reperfusion applied at the end of the 30 min ischaemic period. C group: there are no difference from B, but Akt inhibitor Wortmannin was given for the first 15 min of reperfusion (10^{-7} mol/l). The myocardial injury was evaluated by

the levels of LDH and CK in the coronary effluent. Ventricular haemodynamic parameters were also measured, include HR, LVSP. Left ventricular myocardial was separated and cut to 5 slice, the myocardial was used for myocardial infarction size evaluated with TTC stained. The expression of GRP78 mRNA was detected by reverse transcription PCR (RT-PCR). CHOP, CRT expression and caspase-12 activation were detected using Western blot analysis. Variables were analysed by one-way ANOVA for multiple comparisons, and a P value<0.05 was considered significant.

Results (1) Ischaemic postconditioning reduced LDH, CK and improved the haemodynamic parameters, and reduced myocardial infarction size (22.60±4.3% vs 56.76±5.1%; 54.56±7.2%, p<0.01). (2) IPO on ERs molecules: I/R induced upregulation of GRP78 mRNA, CHOP, CRT expression and caspase-12 activation, and IPO can increase the upregulation of GRP78 mRNA, and relieve CRT over-expression and caspase-12 activation induced by I/R. (3) Wortmannin diminished the effect of IPO.

Conclusion IPO may protect myocardium in isolated rat heart from I/R injury. IPO can increase the upregulation of GRP78 mRNA, and relieve CRT over-expression and caspase-12 activation induced by I/R. Wortmannin diminished the effect of IPO on the activation of CHOP, caspase-12 and GRP78. These results suggest that IPO protects cardiomyocyte from I/R injury by suppressing ERs-induced apoptosis and PI3K/Akt signaling pathway is involved.