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DIABETIC CARDIOMYOPATHY ATTENUATING ERYTHROPOIETIN-INDUCED CARDIOPROTECTION AGAINST ISCHAEMIC-REPERFUSION INJURY VIA RISK PATHWAY

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Objectives Activation of the reperfusion injury salvage kinase pathway (RISK), as phosphatidylinositol 3-kinase/Akt (PI3K/Akt), is a strategy aimed at decreasing cardiac damage in AMI. Erythropoietin (EPO) can activating the RISK pathway by EPO receptors in cardiomyocytes and have demonstrated EPO's cardioprotective effects in myocardial reperfusion against ischaemia-reperfusion (I/R) injury through RISK pathway activation. As RISK has been reported to be impaired in diabetes. In this study we examined whether EPO-induced cardioprotection was maintained in rat models of type 2 diabetes.

Methods Diabetic cardiomyopathy rats was induced by intraperitoneal streptozotocin (STZ, 40 mg/kg) injection. One-week following STZ injection, and blood glucose levels >120 mg/dl were included in the study. High-fat diet rats (HFD) receiving high-saturated-fat diet consisting of 35% fat, 35% carbohydrates, and 22% protein for 4 weeks. Hearts were rapidly excised and immediately mounted on Langendorff-perfusion apparatus. Perfusion was maintained at a constant pressure of 75 mm Hg. Isolated hearts were obtained from two groups: healthy controls (n=10), streptozotocin (STZ) +HFD-induced diabetes (n=12). All hearts underwent 25 min ischaemia and 30 min or 120 min reperfusion. They were assigned to receive either no intervention or a single dose of EPO at the onset of reperfusion.

Results In hearts from healthy controls, EPO decreased infarct size (12.89±0.49 and 42.36±3.28% of left ventricle in EPO-treated and untreated hearts, respectively, $p<0.01$) and increased phosphorylated forms of Akt, and their downstream target GSK-3b. In hearts from STZ+HFD-induced diabetic rats, EPO did not decrease infarct size (41.15±3.21 and 39.23±2.11% in EPO-treated and untreated diabetic rat hearts, respectively, NS) nor did it increase phosphorylation of Akt, and GSK-3b. Administration of GSK-3b inhibitor SB216763 was cardioprotective in healthy and diabetic hearts.

Conclusions STZ+HFD-induced diabetes abolished EPO-induced cardioprotection against I/R injury through a disruption of upstream signalling of GSK-3b. Direct inhibition of GSK-3b may provide an important strategy to protect diabetic hearts against I/R injury.