ERYTHROPOIETIN ENHANCES ARGINASE II ACTIVITY AGAINST NITRIC OXIDE SYNTASE MEDIATED NITROSATIVE STRESS IN RAT POST-ISCHEMIC HEARTS

ACC Poster Contributions
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Background: It had been proved Erythropoietin (EPO) activates Jak2 to protect myocardium against ischemia/reperfusion (IR) injury. However, whether EPO affects dysfunction of myocardial nitric oxide (NO) system is unclear.

Methods: IR was induced in rat heart in Langendorff apparatus by 40 min of stopped perfusion and 120 min of reflow. EPO and/or inhibitors were applied 5 min before reperfusion. Arginase II siRNA was given at baseline to specifically knockdown protein expression.

Results: Compared to untreated hearts, EPO given in IR hearts significantly improved left ventricular developed pressure and reduced myocardial injury as LDH release and infarction by TTC staining, this associated with attenuated caspase-3 activation. Excess formation of NO metabolites and nitrotyrosine evidenced as nitrosative stress was markedly suppressed by EPO. EPO given in IR hearts restores EPO content, which in turn recruits STAT3 and ERK signaling to increase arginase II expression and suppress heat-shock protein 90-dependent upregulation of eNOS and iNOS, respectively. Inhibition of STAT3 and ERK further specifically reversed the effects of EPO. Inhibition of arginase activity by BEC or arginase II expression by siRNA totally abrogates EPO-mediated acute protection.

Conclusions: These results suggested that EPO triggers Jak2-STAT3/ERK pathways to rebuild the balance of arginase II and NOS and thus alleviates nitrosative stress, which may be the basis of myocardial protection following acute IR.