**RAPAMYCIN PROTECTS DIABETIC RABBIT HEARTS AGAINST ISCHEMIA/REPERFUSION INJURY BY REGULATING PTEN-AKT SIGNALING**

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**Background:**  Diabetes is a major risk factor for myocardial infarction (MI). Persistent activation of the mammalian target of rapamycin (mTOR) leads to diabetic complications and plays a critical role in myocardial reperfusion injury following MI. mTOR inhibition with rapamycin (RAPA) at reperfusion preserves cardiac function with reduction of myocardial infarction in type 2 diabetic mice. To demonstrate the clinical potential of these novel observations, we examined the effect of RAPA in a conscious diabetic rabbit model of MI and its associated molecular mechanism.

**Methods and Results:**Control (n=12) and diabetic (DM, n=34; induced by alloxan monohydrate treatment) male New Zealand rabbits were subjected to conscious 45 min ischemia and 3 days of reperfusion by inflating/deflating the hydraulic balloon occluder implanted on the top of the coronary artery. RAPA (0.25 mg/kg, i.v.) or DMSO (vehicle) was infused 5 min before reperfusion. RAPA treatment at the onset of reperfusion significantly reduced infarct size and apoptosis as compared to control and DM. Plasma troponin I was also reduced in RAPA-treated diabetic rabbits following I/R injury. Phosphorylation of S6 (marker of mTORC1) was increased, while the phosphorylation of AKT (marker of mTORC2) was reduced following I/R injury in diabetic rabbit heart. Interestingly, RAPA treatment inhibited diabetes-induced phosphorylation of S6, but restored phosphorylation of AKT. Moreover, the cardiac microRNA-302a, a regulator of anti-oxidative and anti-apoptosis through activating AKT signaling, was reduced with a concomitant elevation of its target PTEN following I/R in diabetic rabbit heart. RAPA treatment restored the level of miR-302a and blunted the induction of PTEN.

**Conclusion:** Rapamycin could be a promising drug in attenuation of reperfusion injury in diabetic subjects following acute MI by regulating of microRNA-302a-PTEN-AKT signaling.