**PDE5 INHIBITION IN PROTECTION OF DIABETIC HEART**

**R.C. Kukreja**, S.S. Koka, L. Xi, A. Varma, F.N. Salloum, E.J. Lesnefsky, A. Das

Virginia Commonwealth University Richmond, VA, USA

Obesity and insulin resistance lead to impaired nitric oxide (NO) bioavailability, oxidative stress, chronic inflammation, atherosclerosis and acute coronary syndromes. Hyperglycemia is associated with increased infarct size and higher risk of congestive heart failure in patients. Phosphodiesterase 5 (PDE5) inhibitors including sildenafil, vardenafil and tadalafil protect against myocardial ischemia/reperfusion (I/R) and ischemic cardiomyopathy. Since PDE5 inhibitors increase NO production and improve endothelial dysfunction, we hypothesized that chronic treatment with the long-acting PDE5 inhibitor, tadalafil would protect the diabetic heart against I/R injury. Leptin receptor null (db/db) mice underwent treatment with tadalafil (1 mg/kg) or 10% DMSO for 28 days. The hearts were isolated and subjected to 30 min global ischemia and 60 min reperfusion. Tadalafil treatment significantly reduced fasting glucose and triglycerides. Infarct size was significantly lower in tadalafil treated mice as compared to the control. Circulating TNFalpha and IL-1beta were reduced following tadalafil treatment. Sirt1, a histone deacetylase that regulates peroxisome proliferator-activated receptor gamma coactivator-1-alpha (PGC-1alpha) which is a master regulator of mitochondrial biogenesis and co-activator of transcription factors impacting energy homeostasis. Our results showed that tadalafil treated mice had significantly higher plasma levels of NO and increased expression of myocardial Sirt1as well as PGC1alpha. Furthermore, tadalafil treatment attenuated ROS production and improved mitochondrial dysfunction as demonstrated by preservation of oxidative phosphorylation with the complex I substrate, glutamate. We conclude that chronic treatment with tadalafil protects against I/R injury in diabetic heart through mechanisms which blunt inflammation and activate NO-induced Sirt1/PGC-1alpha signaling. We conclude that tadalafil could be an attractive therapy for reducing cardiovascular risk factors while providing cardioprotective effect in diabetic patients.