Increased Protein O-GlcNAcylation is Associated with Right Ventricular Dysfunction in Pulmonary Arterial Hypertension

Lauren Rose, BS1, Lian Tian, PhD2, Danchen Wu, MD, PhD2, Thenappan Thenappan, MD1, Nathan Holthaus, BS1, Stephen Archer, MD2, and Kurt Prins, MD, PhD1

1. Cardiovascular Division, University of Minnesota
2. Department of Medicine, Queen’s University

Introduction: The hexosamine biosynthetic pathway (HBP) converts glucose to the monosaccharide uridine diphosphate N-acetylglucosamine (UDP-N-acetylglucoasmine). UDP-N-acetylglucoasmine can function as a signaling molecule by regulating function of multiple proteins via O-glycosidic linkage to serine or threonine residues in a process known as protein O-GlyNAcylation. While numerous studies show glucose uptake is dramatically increased in the right ventricle (RV) in pulmonary arterial hypertension (PAH), the subsequent effects on HBP and protein O-GlyNAcylation in the RV are unexplored.

Methods: Metabolomics and Western blot analysis were used to quantify UDP-N-acetylglucoalsonine levels and total protein O-GlyNAcylation in control and monocrotaline (MCT) rats respectively. Echocardiography was used to characterize RV function in rats. Finally, to indirectly examine the relationship between protein O-GlyNAcylation and RV function in PAH patients, the presence of diabetes and the relationship between hemoglobin A1C (HgbA1C) and RV function was examined in non-Scleroderma PAH patients from the University of Minnesota PH clinic. Dp/dt\text{max}/instantaneous pressure (IP) was calculated from RV pressure tracings to estimate RV contractility.

Results: UDP-N-acetylglucosamine is significantly elevated in the RV of MCT rats (2.4±0.8 fold increase, \(p<0.001\)) and is negatively correlated with cardiac output (\(r=-0.78, p<0.001\)) and tricuspid annular plane systolic excursion (\(r=-0.72, p=0.002\)). Total protein O-GlyNAcylation is increased in the RV (2.8±0.9 fold increase, \(p=0.005\)) but reduced in the left ventricle (0.59±0.19 fold decrease, \(p=0.04\)) of MCT rats. In PAH patients, HgbA1C is negatively correlated with dp/dt\text{max}/IP (\(r=-0.48, p=0.05\)) and diabetic patients have a significant reduction in dp/dt\text{max}/IP (12.5±4.8 vs 17.2±5.9 s\(^{-1}\), \(p=0.02\)) despite no differences in pulmonary arterial compliance (1.8±1.3 vs 1.6±1.3 mL/mm Hg, \(p=0.64\)) or pulmonary vascular resistance (8.8±5.7 vs 10.2±5.7 Wood units, \(p=0.31\)).

Conclusions: Elevated protein O-GlcNacylation is associated with RV dysfunction in PAH. Further studies are needed to determine if inhibition of protein O-GlcNacylation could represent a novel therapeutic strategy to improve RV function.