Ashley Pietra –Annual Virtual Student Research Forum 2024 Abstract

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Title: Circulating Factors in Single-Ventricle Congenital Heart Disease Promote Pathological Metabolic Remodeling in Cardiac Myocytes, Which is Abrogated with Phosphodiesterase-5 Inhibitor Therapy

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Introduction: While operative and perioperative care continues to improve for single ventricle heart disease (SVHF), the 10-year survival in this population is only 39-50%. Phosphodiesterase-5 inhibitors (PDE5i) are increasingly used in this population, however there are currently no proven medical therapies for SVHF. Our group has previously demonstrated that SVHF myocardium is characterized by increased PDE5 activity and impaired mitochondrial bioenergetics, however little is known regarding myocardial effects of PDE5i therapy. We hypothesize SVHF serum circulating factors are distinct from healthy controls and contribute to cardiomyocyte metabolic dysfunction, thereby promoting heart failure progression. Additionally, we hypothesize that PDE5i abrogates these pathologic metabolic alterations.

Methods: Mass spectrometry-based proteomics and metabolomics were performed on healthy control and SVHF patient sera. Using an established novel *in vitro* model, primary cardiomyocytes (neonatal rat ventricular myocytes, NRVMs) were treated with serum +/- 1.5μM PDE5i for 72 hours. In NRVMs, the Seahorse Bioanalyzer was used to assess mitochondrial bioenergetics and mass-spectrometry was used to assess lipid and metabolite profiles.

Results: Unbiased proteomic and metabolomic analysis suggests the serum circulating peptide and metabolite milieu in SVHF is significantly altered, including significant dysregulation of pathways involved in mitochondrial metabolism, glycolysis, amino acid metabolism, oxidative stress, and inflammation. Additionally, SVHF serum circulating factors pathologically remodel cardiomyocytes, including decreased cardiolipin and phosphatidylglycerol lipid species, and shifted metabolite profiles suggesting altered glycolysis, CoA biosynthesis, oxidative phosphorylation, and fatty-acid beta-oxidation. Importantly, PDE5i treatment abrogates the SVHF serum-induced changes in phosphatidylglycerol, and in various metabolites, including in glucose-6-phosphate, pyruvate, and L-carnitine.

Conclusions: Together, these data suggest PDE5i therapy has direct myocardial effects, and likely contributes to beneficial cardiomyocyte metabolic remodeling in SVHF.