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THE ROLE OF THE PENTOSE PHOSPHATE PATHWAY IN LVAD-INDUCED MYOCARDIAL RECOVERY FROM HEART FAILURE

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Heart failure is a crippling disease that has a high prevalence of 2-3% within the United States. A common therapeutic treatment for heart failure (HF) is mechanical unloading by Left Ventricular Assist Devices (LVADs). It has been reported that LVAD treatment leads to improvements in the cardiac function of a subset of HF patients (responders). Glucose via glycolysis serves as the major energy substrate in failing hearts, however studies show that upon LVAD unloading, glycolytic intermediates do not enter the TCA cycle. We hypothesize that glucose is channeled into accessory cardio-protective/repair pathways such as the pentose phosphate pathway (PPP) to facilitate the myocardial recovery seen in responders to LVAD treatment. To investigate this hypothesis, we obtained myocardial tissue samples from HF patients at the times of LVAD implantation (pre-LVAD) and LVAD explantation or cardiac transplantation (post-LVAD); as well as, control samples (donors) from non-failing rejected hearts. The tissue samples were then analyzed using gas chromatography-mass spectrometry (GC-MS) to determine metabolite levels, RNA sequencing to determine transcription levels, and western-blot technique to determine the abundance of enzymes involved in PPP. Although the metabolomics studies are still currently being processed, a preliminary dataset with a smaller sample size shows a trend towards increased PPP metabolites in post-LVAD responders. Western-blot analysis shows that glucose-6-phosphate dehydrogenase (G6PDH) and transketolase (TKT), major enzymes in the PPP, are significantly increased in post-LVAD responders. Furthermore, TKTL1 mRNA expression is upregulated in post-LVAD responders. These results suggest that more glucose is being shuttled into the PPP, which leads to increased cardiac recovery in responders. However, corresponding results from the full metabolomics study are needed to strengthen this claim. In the future, metabolic flux studies using stable isotope ^{13}C-glucose tracers are planned to track the precise pathways of glucose metabolism.