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## THE ONE-CARBON PATHWAY AND CARDIAC FUNCTION RECOVERY FOR HEART FAILURE PATIENTS ON LVAD TREATMENT

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A substantial portion of the world population suffers from chronic heart failure. Mechanical unloading by way of a left ventricular assist device has been shown to be an effective interventional treatment. Most of the heart failure patients on LVAD continue to show HF symptoms and worsening of the cardiac functions (non-responders), however a subgroup of patients have been observed to show substantial recovery in cardiac functions (responders). Metabolic and energy balance perturbations occurring during mechanical unloading have been implicated in these responses. Prior studies have revealed that LVAD-induced mechanical unloading causes an increase in glycolysis without a concomitant increase in TCA cycle activity. One possible explanation is that the pyruvate, produced from glycolysis, is being funneled into beneficial alternative pathways, such as pathways generating precursors for macromolecules required for repair/ maintenance of cellular functions or critical mediators of redox homeostasis like NADPH. *We hypothesize that the glycolytic intermediates are channeled into cardioprotective and repair pathway of one-carbon metabolism, resulting in the cardiac recovery response.*

To test this hypothesis, we performed metabolomic analysis using GC-mass spectrometry (GC-MS), RNA sequencing, and western blot analysis on human cardiac tissue samples obtained at the time of the LVAD implant (pre) and at the time of heart transplant or LVAD explant (post); and control samples (donors) acquired from non-failing hearts. The preliminary metabolomics data indicates that there is an upregulation of one-carbon metabolites, serine and glycine in the responders and downregulation in non-responders post-LVAD. RNA sequencing data found no significant difference between RNA transcription between responders and non-responders, but a general increase compared to donors. Furthermore, western blot analysis of the key enzymes involved in one-carbon metabolism, PHGDH and SHMT1 shows that responders had a significantly higher concentration compared to non-responders post-LVAD. Since, the one-carbon metabolism is one of the major sources for NADPH generation, which can protect cell from damage by free radicals and reactive oxygen species, we also examined the levels of NADPH using an assay kit. As expected, the levels of NADPH were higher in post-LVAD responders compared to non-responders. Although data analysis from GC-MS with a larger sample size is currently in progress, the findings from preliminary metabolomics dataset and western blots indicates the association of increased one-carbon metabolism to cardiac recovery in post-LVAD patients.

In future, highly innovative *in vivo* metabolic flux studies using  $C^{13}$ -stable isotope tracers will be employed to precisely delineate the fate of glucose into one-carbon metabolism. This project will help us to understand the metabolic adaptations in the recovering heart and will pave way new treatments that target pathways leading to repair of the myocardium. The goal is to intervene in patients with no signs of cardiac recovery after LVAD unloading to mimic the metabolic profile/biology of responders.