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CICMD Early Career Symposium Abstract for Oral Presentation:

Title: A **BOLD** Approach to Uncover Mechanisms Driving Hepatic Oxygen Handling in Response to Acute Glucose Stimulus

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Abstract:

Background: Oxygen consumption in the electron transport chain is the terminal step of mitochondrial oxidative phosphorylation (OXPHOS) and a direct readout of mitochondrial function, and its ability to produce adenosine triphosphate (ATP). The liver is a pivotal metabolic hub that uptakes ~33% of post-prandial carbohydrates with capabilities to oxidize and store glucose. Despite only comprising 2-3% of total body mass, the liver utilizes 20-30% of resting energy expenditure and ~20% of circulating oxygen through its roles in nutrient and metabolic regulation. While hepatic oxygen consumption rate (OCR) has been extensively studied in health and disease, the molecular mechanisms governing hepatic oxygen dynamics in response to varied glucose availability remains unclear.

Methods: Oxygen-sensitive magnetic resonance imaging (MRI) techniques are well-established in neuroscience for mapping brain activity and oxygen metabolism, and have found application in the muscle, kidney, and liver. Blood-oxygen-level-dependent (**BOLD**) MRI provides an indirect measure of oxygen delivery to tissues via T_2^* driven changes caused by paramagnetic properties of deoxyhemoglobin. By supplying an Intravenous glucose stimulus (1g/kg), **BOLD** signal responsively decreases. To elucidate mechanisms governing this **BOLD** response, we performed ex vivo liver perfusions and measured OCR via Clark Electrode and traced the samples with 6mM (physiological) or 30 mM (maximal concentration from tolerance tests) [U-^{13}C]glucose and used metabolic flux analyses to understand uptake and utilization.

Results and Impact: Data reveals a detectable response and recovery in **BOLD** signal upon acute glucose stimulus. Complimentary results were observed during ex-vivo liver OCR as well. Furthermore, ^{13}C tracer-based metabolomics analysis will further elucidate governing mechanisms of glucose handling in response to substrate availability. Ultimately, these data lay groundwork to monitor hepatic oxygen dynamics in a spatial, non-invasive, and cost-effective manner and has implications as a metabolic-focused diagnostic and disease-monitoring tool across an array of metabolic liver diseases.