mice fed the KD than GBD- and WD-fed mice, providing increased substrate for chylomicron formation and secretion. Interestingly, KD feeding significantly enhanced intestinal-TG secretion rates in male but not female mice and KD-refeeding after a 12-hour fast led to significant jejunal TG accumulation in female mice compared to GBD- and WD-refeeding but not in male mice suggesting female mice. KD feeding lengthened the small intestine in male mice, whereas in female mice, jejunal villi length increased compared to GBD- and WD-fed mice.

CONCLUSION: Overall, KD feeding promotes functional changes to lipid mobilization and distinct morphological alterations to the small intestine compared to the WD diet over three weeks of feeding. Moreover, changes to intestinal lipid handling in response to KD feeding manifest differently in male and female mice. The contribution of elevated postprandial lipid secretion observed with a ketogenic diet on metabolic health and its impact on atherogenesis remains to be determined.

Canadian Institutes of Health Research - Doctoral Research Award, Canadian Institutes of Health Research - Operating Grant, Ontario Graduate Scholarship

Trainee Research Award Finalist—Basic Science

P014
KETONE ESTER THERAPY REDUCES CARDIAC INFLAMMATION AND CARDIAC DYSFUNCTION IN SEPSIS

S Soni, M Martens, S Takahara, H Silver, M Ferdaoussi, J Dyck

Edmonton, Alberta

BACKGROUND: Sepsis is the body's reaction to an infection that often causes lasting cardiac damage and multi-organ injury due to a dysregulated inflammatory response. Currently, there are no effective treatments to reduce inflammation during sepsis and assist in preventing the lasting cardiovascular damage. Not only are sepsis outcomes worse for cardiovascular disease patients, but the permanent organ damage to sepsis survivors also makes them more susceptible to diseases such as heart failure. Thus, therapeutic strategies to reduce the inflammatory response in sepsis are needed to mitigate the development of cardiovascular disease and improve the outcomes and quality of life for cardiovascular patients who survive sepsis. Herein, we tested the efficacy of a therapy that increases circulating ketones via ketone ester supplementation. Ketones are small molecules that are normally produced by the liver and are elevated during low-carbohydrate states, such as fasting. While ketones are classically known to be metabolic substrates that produce ATP, they also have non-metabolic effects, such as inhibiting inflammation. Thus, we hypothesized that ketones have anti-inflammatory effects which will protect against sepsis-induced cardiac dysfunction in a mouse model of sepsis.

METHODS AND RESULTS: To determine the effects of ketone therapy in sepsis, 8-week-old mice orally received vehicle or a clinically tested ketone ester (KE) for 3 days. On day 3, mice were injected with saline or lipopolysaccharide (LPS), and cardiac function, cardiac inflammation, as well as systemic inflammation and multi-organ injury were assessed 24 hours post-injection. Vehicle-treated LPS mice had higher blood ketones compared to non-septic controls, suggesting that ketones may be important as an innate defense mechanism. This response was further increased in KE-treated LPS mice. While vehicle-treated LPS mice had an induction of cardiac and systemic inflammation (e.g., IL-1β, IL-6), most inflammatory markers were significantly lower in KE-treated LPS mice. Similarly, KE-treated septic mice had lesser cardiac dysfunction than vehicle-treated septic mice. These anti-inflammatory effects were also observed in other vital organs such as the kidney and liver thereby demonstrating that KE therapy had global protective effects. Lastly, ketolytic enzymes were reduced or unchanged in vehicle- and KE-treated septic mice, potentially ruling out a normalization of ketone metabolism as a mechanism by which KE treatment may improve function.

CONCLUSION: Together, these data show that ketone therapy may be a novel translational approach to reducing cardiac and systemic inflammation, as well as cardiac dysfunction in a model of sepsis.

Canadian Institutes of Health Research - Doctoral Research Award, Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation of Canada

P015
LARGE ANIMAL MODEL OF DONATION AFTER CIRCULATORY DEATH AND NORMOTHERMIC REGIONAL PERFUSION FOR CARDIAC ASSESSMENT

K Khalil, R Ribeiro, J Alvarez, M Badiwala, S Der Sarkissian, N Noiseux

Montréal, Québec

BACKGROUND: The increase in demand for cardiac transplantation throughout the years has fueled interest in donation after circulatory death (DCD) to expand the organ donor pool. However, the DCD process is associated with the risk of cardiac tissue injury due to the inevitable period of warm ischemia. Normothermic regional perfusion (NRP) allows for an in-situ organ assessment, allowing the procurement of hearts determined to be viable.

METHODS AND RESULTS: Here, we described a clinically relevant large animal model of DCD followed by NRP. Circulatory death was established in anesthetized pigs by stopping mechanical ventilation. After a preset warm ischemia period, an extracorporeal membrane oxygenator (ECMO) was used for a NRP period lasting at least 30 min. During this reperfusion period, the model allowed the collection of various myocardial biopsies and blood samples