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EXPLORING THE IMPACT(S) OF MICROGRAVITY AND HYPOXIA ON VASCULAR FUNCTION USING HINDLIMB UNLOADING MODEL: A JOINT MOHAMMED BIN RASHID SPACE CENTER AND EUROPEAN RESEARCH INSTITUTES PROJECT

Abstract

The mechanisms of the vascular damage in the spaceflight's environment are not clearly understood. This unique project, sponsored by the Mohammed Bin Rashid Space Center, UAE partners along with European partners from Austria and Belgium, will investigate the impact of microgravity and hypoxia on vascular health in hindlimb unloading (HLU) rodent model. HLU has been used extensively to demonstrate the effects of unloading, as well as to simulate the effects of cephalad fluid shifts as seen during spaceflight. The overarching hypothesis that will be tested is that the cephalad fluid shifts, together with other factors in the spaceflight's environment, especially hypoxia, result in vascular damage, including endothelial dysfunction and angiogenesis. Specifically, we will assess the time course of endothelial dysfunction and angiogenic parameters during HLU. The endothelial cells (ECs) of those mice will be harvested and their genomic, transcriptomic and proteomic signatures will be examined and compared between mice subjected to low or normal gravity as well as to hypoxic or normoxic conditions. The hindlimbs of mice, will be elevated so that approximately 30 head-down tilt occurs, thus causing headward shifts in fluids and unloading of the weight from the hind limbs. Four groups of mice with different conditions to simulate the spaceship environment will be used: 1) No hindlimb unloaded condition (+ Gravity) plus normoxia; 2) No hindlimb unloaded condition (+ Gravity) plus hypoxia; 3) Hindlimb unloaded (HLU) condition (- Gravity) plus normoxia; 4) Hindlimb unloaded (HLU) condition (- Gravity) plus hypoxia. The time course of sampling will be as follows: Baseline, following 1, 3, 7, 14, 21 day(s) of HLU and during recovery +1 day and recovery 3 days. The basic measurements of the blood pressure and vascular changes in these mice will be conducted using non-invasive measurements. The endothelial cells (ECs) will be isolated and then further transcriptome analysis carried out. Special attention will be given to genes and biomarkers involved in EC activation and inflammatory status (interleukins, VCAM-1, ICAM-1), senescence, barrier function (junctional molecules), vasoregulation, etc. In particular, alterations in the expression of metabolic pathway genes will be investigated (glycolysis, fatty acid oxidation, glutamine metabolism, mitochondrial function, redox homeostasis, etc.). The results of this proposal are particularly

important for understanding the timing and the molecular mechanisms of vascular dysfunction in HLU model that simulate astronaut environment in spaceflight.