Fiscal Year:	FY 2022	**Task Last Updated:**	FY 06/14/2022
PI Name:	Zawieja, David Ph.D.		
Project Title:	Effects of Microgravity on Ocular Vascular Hydrodynamics		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	77807	**Congressional District:**	31
Comments:			
Project Type:	FLIGHT	**Solicitation / Funding Source:**	2017-2018 HERO 80JSC017N0001-BPBA Topics in Biological, Physiological, and Behavioral Adaptations to Spaceflight. Appendix C
Start Date:	12/21/2018	**End Date:**	12/20/2022
No. of Post Docs:	4	**No. of PhD Degrees:**	10
No. of PhD Candidates:	1	**No. of Master' Degrees:**	1
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	2
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA JSC
Contact Monitor:	Stenger, Michael	**Contact Phone:**	281-483-1311
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 12/20/2022 (original end date was 12/20/2021) per NSSC information (Ed., 1/4/22)		
Key Personnel Changes/Previous PI:	2023 Update: As Principal Investigator (David Zawieja, Ph.D.) is retiring from Texas A&M University, the new PI for this project will be Travis Hein, Ph.D. (also at Texas A&M University). Dr. Zawieja will remain as a CoInvestigator on the project. 2022 Update: Former PI (Dr. Anatoliy Gashev M.D., Ph.D.) unexpectedly passed away in August 2021. His technician still worked on this project.		
COI Name (Institution):	Loerch, Linda M.S. (NASA Johnson Space Center) Tharakan, Binu Ph.D. (Scott & White Memorial Hospital) Macias, Brandon Ph.D. (NASA Johnson Space Center) Lee, Stuart Ph.D. (Wyle Laboratories, Inc./NASA Johnson Space Center) Hein, Travis Ph.D. (Texas A&M University System) Bagher, Pooneh Ph.D. (Texas A&M University System)		
Grant/Contract No.:	80NSSC19K0392		
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Task Description:	Spaceflight-associated neuro-ocular syndrome (SANS) is reported to affect ~40% of astronauts completing long-duration spaceflights (as of May 2017) and has been characterized as the development of one or more findings: optic disc edema, hyperopic shifts, globe flattening, cotton-wool spots, or choroidal folds. The leading hypothesis for the development of ocular changes is that prolonged exposure to the headward fluid shift that occurs in weightlessness is the primary instigating factor, and additional factors such as genetic disposition, ambient CO2 on the International Space Station, or on-orbit exercise countermeasures may augment or diminish the development of ocular symptoms. However, the pathophysiology of SANS remains unclear. Evidence for the contribution of intracranial pressure alone in SANS is controversial. Therefore, studies of ocular vascular hydrodynamics are required to clarify if chronic mild elevations of ocular pressure variables compromise ocular structure and function. Since all blood and lymph vessels are compliant, fluid-filled structures whose pressures are strongly influenced by gravity, we propose to focus our studies on the potential changes directly to the ocular vasculature caused by microgravity. Perfusion of the optic nerve and inner retina for sufficient delivery of oxygen and nutrients is dependent on retinal blood flow. The pressure gradient for driving blood flow through the inner retina begins with the arterial pressure in the feed artery, which is the central retinal artery in humans. Changes in retinal blood flow or pressure may contribute to the formation of cotton wool spots and optic disc edema. Optic disc edema, choroidal folds, and optic nerve thickening may also result from ocular venous congestion and/or elevated venous compliance, disruption of the blood-retinal barrier, and/or reduction in ocular lymph flow. There has been no systematic analysis of the ocular vascular changes in microgravity. We have assembled a team of experts in SANS and all 3 main vascular types (arteries, veins, and lymphatics) to address this information gap. Thus, the objective of this application is to determine whether microgravity alters the structure and function of the ocular vasculature at the level of feed arteries, venous exchange and capacitance vessels, and lymph vessels. This provides a novel comprehensive evaluation of the ocular vascular elements. The central hypothesis of this proposal is that microgravity/spaceflight-induced changes in the structure/function of the ocular vasculature lead to alterations in ocular hydrodynamics and promote symptoms of SANS. We will accomplish this objective using in vivo measures of vascular function (retinal artery blood flow, retinal arteriole and venular diameter measurements, and retinal venular permeability measures) and in vitro studies of freshly isolated vascular structure and function (vessel/tissue histology, arterial vasomotor regulation, venous compliance measures, and lymphatic transport characteristics). These studies will be conducted in mice flown in space and the corresponding ground controls to address the following specific aims: 1: Evaluate the effects of microgravity on ocular artery structure/function. 2: Evaluate the effects of microgravity on ocular vein structure/function. 3: Evaluate the effects of microgravity on ocular lymphatic structure/function. Information from these novel studies will provide the first comprehensive analysis of the effects of microgravity on ocular vascular function where the predominant changes associated with SANS in astronauts occur. It will also help define the roles these may play in the etiology of SANS and could lead to the development of countermeasures for SANS.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The expected findings from the experimental planned for RR23 will also provide new insight into vascular complications relevant to ocular diseases in humans on Earth, such as glaucoma, diabetic macular edema, and ocular hypertension.
Task Progress:	2023 Update: As Principal Investigator (David Zawieja, Ph.D.) is retiring from Texas A&M University, the new PI for this project will be Travis Hein, Ph.D. (also at Texas A&M University). Dr. Zawieja will remain as a CoInvestigator on the project. Spaceflight Associated Neuro-ocular Syndrome (SANS) develops in astronauts completing long-duration spaceflights and is diagnosed based on one or more findings: optic disc edema, hyperopic shifts, globe flattening, or choroidal folds. Prolonged exposure to the headward fluid shift that occurs in weightlessness is regarded as the primary instigating factor for ocular changes, but the pathophysiology of SANS remains unclear. Also, there has been no systematic analysis of the ocular vascular changes in microgravity. The central hypothesis of this project is that microgravity/spaceflight-induced changes in the structure/function of the ocular vasculature, at the level of arteries, veins, and lymphatics, lead to alterations in ocular hydrodynamics and promote signs of SANS. Specific Aim 1: Evaluate the effects of microgravity on ocular artery structure/function. Aim 1A: We completed the in situ studies by performing intraocular pressure (IOP) measurements, optical coherence tomography (OCT) / retinal fundus imaging and Doppler ultrasound measurements in the flight, habitat ground control (HGC) and vivarium ground control (VGC) cohorts of mice. We found that central retinal artery blood flow velocity was lower in the flight mice compared to the HGC and VGC mice. IOP was about 20% higher in the spaceflight mice than in the VGC mice. Data analysis of the OCT images is currently ongoing. Aim 1B: We completed the in vitro studies for assessment of vasomotor function of isolated and pressurized ophthalmic arteries in all 3 cohorts of mice. We found that the dilations of isolated ophthalmic arteries to endothelium-dependent agonist acetylcholine and endothelium-independent agent sodium nitroprusside were not different among cohorts. By contrast, constriction to endothelin-1 was lower in ophthalmic arteries from flight mice. We collected the eyes and plasma from all 3 cohorts of mice and will perform assays to determine the water content/edema (wet-dry ratio) and cytokine/inflammatory protein levels in these samples. Specific Aim 2: Evaluate the effects of microgravity on ocular vein structure/function. Aim 2A: Following the mission to the International Space Station (ISS), vasomotor responses were observed in isolated angular veins from nine C57BL/6J mice using wire myography. The angular vein was mounted on the jaw of a Danish Myotech wire myograph on 15µm gold-plated tungsten wire. Following a normalization procedure, veins were exposed to agonists that allowed for the examination of endothelial cell and smooth muscle cell function. Vivarium controls – consisting of mice of the same cohort housed in conventional vivarium cages; and habitat controls – consisting of mice housed in specially designed habitats exposed to similar CO2 levels, temperatures, etc., as on the ISS; were used for comparison. Preliminary analysis demonstrates that vasoconstriction to the adrenergic receptor agonist was reduced following spaceflight as compared to vivarium controls, with ground controls demonstrating an intermediate response. Vasodilation to an exogenous nitric oxide donor was reduced following spaceflight as compared to both vivarium and ground controls. These data suggest that angular vein function is altered following exposure to the space environment. Aim 2B: We performed experiments to assess the function of ocular veins after 39 days of spaceflight (RR23) in male mice. Retinal microvascular permeability was assessed in vivarium, ground control, and space mice. The mice were

anesthetized with isoflurane and injected (iv) with FITC-dextran-10kDa as an indicator of vascular permeability. This was followed by the imaging of the retinal venules for FITC-dextran extravasation under a multi-photon microscope. We observed significant increase in vascular permeability in the flight group compared to the vivarium group after FITC-dextran injection. We also observed an increase in permeability in the flight group compared to the ground control group that was not significant statistically. The ocular tissue from another set of mice from each group were collected and processed for immunohistochemistry and molecular biology studies. The work is currently in progress for evaluating the changes in localization and expression of blood-retinal barrier (BRB) tight junction proteins (zonula occludens-1, claudin-5, and occludin).

Specific Aim 3: Evaluate the effects of microgravity on ocular lymphatic structure/function. ~40% of the ocular lymphatics in the flight mice had no phasic pumping activity, whereas ~80% of all of the control groups did.

There was no significant change in the resting tone of the lymphatics in flight versus controls, but there was a complete loss of the shear-induced inhibition of tone seen in normal/controls.

There were trends towards: increased lymph pump contractions frequency, decreased pump amplitude, and impaired flow/shear-dependent impact on the lymph pump amplitude and flow in flight versus controls.

Bibliography Type:	Description: (Last Updated: 04/24/2019)